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Attention: Section 8(e) Coordinator (CAP Agreement)

Dear Sir/Madam:

The enclosed study/report is submitted to EPA in accordance with the requirements and established guidelines of the TSCA Section 8(e) Compliance Audit Program (CAP). We do not consider any of the documents submitted under the CAP to be Confidential Business Information.

Company Name:	ICI AMERICAS INC.
CAP Identification Number:	8ECAP-0040
Address:	WILMINGTON, DE 19897
Telephone Number:	(302) 886-5503
Chemical/Mixture Identity:	Tolylene Di-isocyanate
CAS Registry Number(s):	26471-62-5
Study/Report Number:	CTL/T/1286
Study/Report Title:	3 Week Inhalation Toxicity in the Rat
Study/Report Summary:	SUMMARY ATTACHED
Previous Submission Type & Document Control No.:	N/A

Sincerely,

Samuel E. Malovrh

S. E. Malovrh
Director, Environmental Affairs

R

IMPERIAL CHEMICAL INDUSTRIES LIMITED
CENTRAL TOXICOLOGY LABORATORY
ALDERLEY PARK MACCLESFIELD CHESHIRE UK

CATEGORY B REPORT (CONFIDENTIAL)
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CTL Ref: Z1285
CTL Study No: MR0001
Copy No: 19

REPORT NO: CTL/T/1286

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

Repeated

by

I P Bennett
I S Chart
J E Doe
C W Gore
D S G Patton

2 Jan 92

Preliminary Report

Issued by:

Date of Issue: - 2 FEB 1990

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

SUMMARY

1. Groups of 8 male and 8 female rats were subjected to fifteen exposures of TDI vapour, each of six hours duration over a period of three weeks. The concentrations were:

Group I - air controls
Group II - 0.24ppm
Group III - 0.67ppm
Group IV - 2.83ppm

2. Pulmonary function, haematology, clinical chemistry and pathological examinations were made on the rats.

3. The rats exposed to 2.83ppm TDI had reduced pulmonary function and some haematological changes. The other rats showed no changes in these values.

4. On gross examination the lungs of animals exposed to 2.83ppm appeared inflated, some also had reddened patches/areas. Other changes such as a loss of body fat, thymic atrophy and gas and fluid filled intestines were seen in a number of the more severely affected anim[illegible].

Microscopic changes attributable to TDI were seen in the respiratory tract of all animals exposed to TDI. The degree and extent of change varied with the concentrations. In the nasal passages, larynx, trachea and bronchial tree the changes seen consisted of epithelial necrosis with reparative hyperplasia and squamous metaplasia. These were accompanied by varying degrees of inflammatory response. In the lung parenchyma some damage occurred to the alveoli - this consisted of collapse, oedema/fibrin deposition, histiocytosis, chronic interstitial inflammatory infiltration and/or fibrosis of alveolar septa, acute alveolitis and some epithelialisation in animals exposed to atmospheres of 0.67ppm and above.

The rats exposed to 0.24ppm TDI showed signs of minimal nasal irritation, which can be attributed to some of the large excursions in concentrations which occurred during the experiment.

5. TDI is corrosive to the respiratory tract, causing severe toxicity at 2.83ppm. The no effect level is under 0.24ppm but is probably close to this value.

IMPERIAL CHEMICAL INDUSTRIES LIMITED
CENTRAL TOXICOLOGY LABORATORY
ALDERLEY PARK MACCLESFIELD CHESHIRE UK

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REPORT NO: CTL/T/1286

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

Repeated

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Date 2 Jan 92

Signature J P Lyon

by

I P Bennett
I S Chart
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C W Gore
D S G Patton

Preliminary Report

Issued by: J.L.H.

Date of Issue: - 2 FEB 1980

CTL/T/1286

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT.

We, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the above study.

I P Bennett	Study Investigator	I Bennett	4:2:80
J E Doe	Study Manager	J E Doe	28 JAN 80.
D S G Patton	Pathologist	p p D S G Patton	1:2:80.
I S Chart	Haematologist	I S Chart	29.1.80.
C W Gore	Clinical Chemist	C W Gore	7.2.80

CTL/T/1286

TOLYLENE DI-ISOCYANATE
THREE WEEK INHALATION TOXICITY IN THE RAT

CONTENTS

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5. TDI is corrosive to the respiratory tract, causing severe toxicity at 2.83ppm. The no effect level is under 0.24ppm but is probably close to this value.

1. INTRODUCTION

Tolylene di-isocyanate (TDI) is widely used for the manufacture of polyurethane products. It is known to cause respiratory sensitization in a proportion of those exposed to it, consequently it has a low TLV of 0.02ppm. The acute toxicity has recently been re-assessed (as part of Project A7) in these laboratories, and the 1 hour LC50 was determined as 66ppm. Most of the rats died within 36 hours of exposure and the lung appeared to be the target organ.

The 1 hour LC50 provides data to evaluate the hazard of accidental spillages, but it does not provide information about the effects of repeated exposure, which may be experienced in the work place. The 1 hour LC50 is below the saturated vapour concentration at 20°C, but it is necessary to determine the effects of multiple exposures to lower levels to try to determine a no effect level.

The sub-acute toxicity of TDI has been studied previously (Henck et al 1976) but that study was intended to be a sighting study for the long term study being undertaken at Hazelton Laboratories (Europe) and the animals were exposed to the relatively low concentrations of 0.3 and 0.1ppm. The rats in the study reported here were exposed to a wider range of concentrations. This study also formed part of a programme (Project A7) designed to investigate the toxicity of phenylisocyanate (PhI) and diphenyl di-isocyanato-methane (MDI).

This study started on 2nd August 1977.

2. MATERIALS AND METHODS

2.1. Tolylene Di-isocyanate

Tolylene Di-isocyanate, as SUPRASE EN, (Batch A8H 2146) a mixture of 80% of the 2,4 isomer and 20% of the 2,6 isomer, was supplied by Imperial Chemical Industries Ltd, Organics Division, Blackley (see Appendix 8). The sample was given CTL Ref. No. Z1285.

2.2 Atmosphere Generation

Atmospheres containing TDI vapour were generated by blowing clean, dry air through a sintered glass absorber immersed in TDI liquid at room temperature as shown in Fig. 1. The saturated vapour was diluted by direct addition of clean, dry air in a mixing vessel before being led to the exposure chamber. The target concentrations are shown in section 2.6.

2.3. Exposure Chambers

The rats were housed in chambers manufactured from 'Perspex'® during exposure (Gage 1959). The volume of each chamber was 60 litres. The structure (shown in Fig. 1), enables animals to be individually housed during exposure. The total airflow through the chamber was 8 litres/minute.

2.4. Animals

Male and female SPF albino rats of the Alderley Park, Wistar derived strain, weighing 175-215g at the start of the experiment were used. They were housed four to a wire-bottomed cage, with food (Oakes Powder 'O' pellets) and tap water available ad libitum except during exposure periods and the collection of urine after the fifteenth exposure. A copy of the diet analysis forms Appendix 10. The temperature in the laboratory was recorded (see Appendix 11).

2.5. Atmosphere Analysis

The atmosphere was analysed for total TDI content by Marcali's method, according to the method of H.M. Factory Inspectorate; using a Cecil CE292 Digital Ultraviolet Spectrophotometer. The atmosphere in the exposure chambers was analysed at least three times in the course of an exposure. The air sample was drawn through two sintered glass absorbers containing 10ml of absorbtion medium at a rate of one litre/minute for 10 minutes.

During two days (days 7 and 8) of the experiment the chemicals used for

analysis were found to be contaminated and atmosphere samples were trapped in ethanol and analysed by high pressure liquid chromatography (HPLC) at Imperial Chemical Industries Ltd. Organics Division, Blackley at a later date.

2.6. Experimental Design

The cages were randomly assigned to groups 1 to 4 using a table of permutations of the numbers 1 to 4, so there were four cages in each group. The rats were then allocated to groups using the table of permutations. Each cage received one rat and the process was repeated three times. Each treatment group consisted of eight male and eight female rats. Prior to the first exposure the rats were uniquely identified by the attachment of numbered metal tags to their right ears.

The treatment groups consisted of the following animals:

Group	Target Concentration	Male Nos.	Female Nos.
1	Air Control	1- 8	9-16
2	0.1ppm	17-24	25-32
3	0.5ppm	33-40	41-48
4	2.5ppm	49-56	57-64

The total number of rats was too large to be subject to full post mortem examination on a single day, consequently the rats were split into two batches: batch one, consisting of rat nos. 1-4, 9-12, 17-20, 25-38, 33-36, 41-44, 49-52, 57-60, batch two consisting of rat nos. 5-8, 13-16, 21-24, 29-32, 37-40, 45-48, 53-56, 61-64. Batch one was first exposed one day before batch two and each batch was subjected to 15 six hour exposures on the days shown (Table 1).

2.7. Clinical Condition

The animals were examined whilst being placed into and removed from the exposure chambers and daily on those days when they were not exposed. Any abnormalities in clinical condition were noted.

2.8. Body weights

Individual body weights were recorded, using a Torbal Balance PL12/D, on the days shown in Table 1, before exposure.

2.9. Food and Water Consumption

The food and water consumed by the four rats in each cage was measured over an 18 hour period on the nights shown in Table 1.

2.10 Lung Function

The lung function of all the rats was assessed on the days shown in Table 1, before exposure on the days when exposure was due. The non-invasive forced oscillation method described by Swann et al, 1965, and, Hiett, 1974 was used.

2.11. Urine Collection and Examination

At the end of their final exposure period all the rats were placed in metabolism cages in groups of four and allowed water for one hour. After this the water was removed and the urine was collected for 18 hours. The following analyses were made: Volume, Specific Gravity, (using an Atago refractometer), pH, Bilirubin and Glucose (using 'Bili-Labstix', Ames Co) and Protein [using the Biuret method, Clinical Chemistry, Principles and Techniques (1964) Henry RJ, 182].

2.12. Haematology

All surviving rats were bled by cardiac puncture on the day specified for post mortem on the flow chart (Table 1). The blood was examined, and the

following values recorded: Haemoglobin, White cell count, Red blood cell count, Mean cell volume, Mean cell Haemoglobin, Mean cell Haemoglobin concentration, Haematocrit, Differential white cell count and Platelet count (Ref Dacie and Lewis, 5th Ed).

2.13. Blood Biochemistry

Blood was taken by cardiac puncture and analysed for the following parameters: plasma urea (Technicon AAII methodology, Marsh et al 1963), Alanine transaminase, ALT and Aspartate transaminase, AST (measured on the Vitatron 'AKES' using BCL test kits numbers 124656 and 124508), Sodium and Potassium (measured using a Corning 430 Flame Photometer).

The values for each animal were recorded separately.

2.14 Post mortem examination and histopathological evaluation.

Any rats which died during the course of the experiment and all the surviving rats were killed by over exposure to Halothane B.P. ('Fluothane' ICI Ltd), bled for haematological studies and then necropsied. Any macroscopic abnormalities observed at necropsy were recorded. The following organs were examined and removed:

Fixed in formal corrosive and processed to slides: Larynx, Trachea, Thyroids, Diaphragm, Liver (left, right and median lobes), Spleen, Kidneys, Heart, Pancreas, Adrenals, Cervical, Mesenteric and Thoracic Lymph nodes, Mammary Gland, Salivary glands, Oesophagus, Ovaries/Testes, Thymus and Bladder.

The following tissues were fixed in formol saline: Spinal cord, Nasal cavity, Brain, Lungs (weighed and perfused with 2ml/100g following removal of the larynx and thyroids), Sciatic nerve, Eyes and any abnormal tissues or lumps.

These tissues were processed routinely and 5µm paraffin sections cut and stained with haematoxylin and esoin. The sections were then examined by light microscopy. Selected sections were recut and stained with a variety

of stains which included: Periodic acid schiff, Van Kossa silver tuchnique and oil red O.

In addition the following tissues were taken and stored in Formol saline: Pituitary, Aorta (Thoracic), Prostate/seminal vesicles, Small intestine (duodenum, jejunum, ileum), Large intestine (Caecum, Colon) Skeletal Muscle (Thigh), Stomach, Liver (second section), Uterus/Cervix and Epididymis.

2.15 Statistical Methods

Where appropriate means, standard errors of the mean, standard deviations were calculated. Where comparisons are made, Student's t-test was used to demonstrate statistical significance.

2.16 Data Storage

Original data and tissues are stored in Archives, Central Toxicology Laboratories, ICI Limited, Alderley Park, Macclesfield, Cheshire, filed under study No. MR0001. A copy of this report is held in the Reports Centre, Central Toxicology Laboratories, ICI Limited, Alderley Park, Macclesfield, Cheshire UK.

3. RESULTS

3.1. Atmosphere Concentrations

The daily mean atmospheric concentrations are shown in Figs. 2,3,4. The graphs were prepared from the data in Appendix 1 Tables 1. There was considerable variation in all three dose groups, so that the overall experimental mean concentration differed from the target concentration as shown below.

Target Concentration		Actual Concentration
Group 2	0.1ppm	0.24 $\pm$ 0.55ppm low dose
Group 3	0.5ppm	0.67 $\pm$ 0.097ppm middle dose
Group 4	2.5ppm	2.83 $\pm$ 0.235ppm high dose

3.2. Body Weights

The body weights of the rats are shown on Figs 5 and 6. The graphs were constructed from the data in Appendix 1, Tables 2. The body weight gain of groups 2 and 3 was not significantly different from the controls. Both the males and the females of group 4 showed a weight loss after the fifth day of exposure which was not regained during the experiment. The females of group 4 showed further absolute weight loss from day 13 of the experiment.

3.3. Food and Water Consumption

The food and water consumption are shown in Figs 7 and 8. The graphs were constructed from the data in Appendix 1 Tables 3 and 4. Both the food and water consumption of group 4 were depressed compared with the other three groups. The group 3 animals' food consumption was slightly depressed compared with the controls on day 18 of the experiment. The weight loss in the group 4 rats was associated with decreased food intake.

3.4. Clinical observations and mortality

Group 1 - Controls:

No abnormalities were detected in any of the rats at any time during the study. All the animals survived until their scheduled sacrifice date.

Group 2 - low dose:

Rat, No.21 (male, batch 2) had blood around its eyes on 4 August 1977 (Day 1) Blood stains were present on 6 and 8 August 1977 (Days 1 and 3). Blood stains were also noted on 18 August 1977 (Day 13).

All the rats in the group showed laboured breathing after exposure on 12 August 1977 (Days 8/7). There was a large excursion in the TDI concentration on that day (see Fig. 2).

Rats 21-24 (Males, Batch 2) and rats 29-32 (Females, Batch 2) were breathing noisily on 22 August 1977 (Day 17).

All the rats survived to their scheduled sacrifice date.

Group 3 - middle dose:

All the rats in the group had difficulty in breathing on 12 August 1977 (Day 8/7). They all survived to their scheduled sacrifice date.

Group 4 - High dose:

All the rats showed laboured breathing after exposure on:

11 August 1977 - Day 7/6
12 August 1977 - Day 8/7
18 August 1977 - Day 14/13

All the rats had laboured breathing and had blood around their snouts after exposure on:

19 August 1977 - Day 15/14
22 August 1977 - Day 18/17

The rats showed laboured breathing, blood around their snouts and pilo-erection on 23 August 1977 (Day 19/18).

All the rats showed similar symptoms but were also gasping after exposure on 24 August 1977 (Day 20/19).

The following animals did not survive to their scheduled sacrifice date:

Rat 61 (Female, Batch 2) died during lung function assessment on 24 August 1977 (Day 19).

Rat 62 (Female, Batch 2) was killed as moribund on 25 August 1977 (Day 20).

Rat 53 (Male, Batch 2) was found dead 25 August 1977 (Day 20).

Rat 63 (Female, Batch 2) was found dead on 25 August 1977 (Day 20).

The remaining animals were killed on schedule.

3.5. Lung Function Assessment

The lung function results are shown in Figs. 9,10,11,12,13. The data from which these graphs were prepared are contained in Appendix 4, Tables 1-16. There was a progressive change in the results for the rats exposed to top dose. Respiration rate and tidal volume both fell, causing a drop in minute volume. Airways resistance increased and total thoracic compliance decreased. These changes are consistent with the development of nonreversible obstructive changes in the lungs. Neither group 2 nor group 3 differed from the control group in any of the parameters measured.

3.6. Urine Biochemistry

The results of urine analysis are shown in Fig. 14. The data from which these graphs were prepared are contained in Appendix 5, Tables 1 and 2. There was a decrease in urine volume in both group 3 and 4. There was also a decrease in urinary protein which was most marked in group 4 males and group 3 and 4 females.

3.7. Blood Biochemistry

The results of the analysis of blood biochemistry are shown in Figs. 15-16. The data from which the graphs were prepared are contained in Appendix 6, Tables 1-8. There was no difference between the males in group 2, group 3 and group 1. However, the males in group 4 had elevated urea levels. They also showed higher levels of AST and ALT. One rat (Batch 1 No. 50) had very high levels.

Neither the females in group 2 nor the females in group 3 differed from

the controls. The females in group 4 had slightly elevated AST and ALT levels.

3.8. Haematology

Statistical Analysis:

Statistically significant differences were found between the means of the

group 1 and the test animals in the following parameters:

Haemoglobin:

A slight increase in the haemoglobin level was noted in the Group 3 female animals at 21 days but the increase was marked in both the male and female animals in Group 4.

Haematocrit:

The haematocrit was moderately increased in the Group 4 animals at 21 days and the change is haematologically significant.

Red Cell Count:

A moderate increase in the red cell count was seen in the Group 4 animals at 21 days and the change is haematologically significant.

Mean Cell Volume:

The slight decrease in the mean cell volume in the Group 4 animals would not, in isolation, be considered haematologically significant but in view of the other results it must be considered a haematologically significant change.

Mean Cell Haemoglobin:

A slight increase in the mean cell haemoglobin was seen in the Group 2 females but the change is of no haematological significance.

Mean Cell Haemoglobin Concentration:

The mean cell haemoglobin concentration was slightly increased in the Group 2 female animals and moderately increased in both the male and female animals in Groups 3 and 4. The change is haematologically significant.

Total White Cell Count:

There is a marked decrease in the Group 4 males and this change is of haematological significance.

Absolute Lymphocyte Count:

The slight increase in the absolute lymphocyte count seen in the Group 2 females and the slight decreases in the Group 2 males and Group 4 females are not considered to be of haematological significance. However, the moderate reduction observed in the Group 4 males is haematologically significant.

Platelet Count:

The moderate fall in the platelet count observed in the Group 4 males is large enough to be of haematological significance.

Prothrombin Time:

The prothrombin time was slightly prolonged in the Group 4 female animals but the change is not haematologically significant.

The markedly prolonged time in the Group 2 males is difficult to explain.

There is a general slight increase in the time in all the animals in the group although two results (No. 20 and 23) are much larger than the others but the changes are not seen at the higher dose levels.

Kaolin-cephalin Time:

The markedly increased kaolin-cephalin time in the Group 2 males has the same significance as above.

There were no haematologically significant changes in the following parameters: Mean cell haemoglobin, Absolute neutrophil count, Bone marrow.

3.9. Pathology

A summary of the major histopathological findings in selected tissues is presented in Appendix 9.

3.9.1. Necropsy findings: On gross examination the following abnormalities were seen in the lungs of the group 4 animals:

enlarged/inflated lungs in three males and three females.
dark red areas on the lungs of five males and six females.
The lung weights were also significantly different from the rats in group 1, as shown in Fig 17. The data for this figure are presented in Appendix 7 Tables 1-4.

In addition the following were also observed:

Lack of abdominal fat in two males and three females.
thymic involution in three males and four females.
gas and fluid filled intestines in three males and three females.

Dark spots/areas/blotches/consolidation were seen in the lungs of four males and five female rats from group 3.

3.9.2. Histopathology: Lesions attributable to treatment.

Nasal passages.

Marked necrotising rhinitis involving the respiratory and olfactory epithelia with varying degrees of reparative epithelial hyperplasia was seen in all the group 4 animals.

In all the group 3 animals changes ranging from mild acute rhinitis to moderate necrotising rhinitis with some reparative epithelial hyperplasia were seen, while squamous metaplasia and a slight submucosal chronic inflammatory infiltration occurred in nearly half the animals (four males and three females).

In almost all the group 2 animals (8 males and seven females) some epithelial degeneration with a mild to moderate acute rhinitis and reparative epithelial hyperplasia was seen, while squamous metaplasia was observed in one male and two females.

Larynx:

Focal epithelial necrosis/degeneration was seen in several animals (two males and three females) exposed to 2.5ppm TDI while reparative epithelial hyperplasia and squamous metaplasia occurred in half the animals. In one male and four female rats mild acute laryngitis was also observed.

In half the males and six of the females exposed to 0.5ppm TDI reparative epithelial hyperplasia was seen; in three animals (one male and two females) squamous metaplasia was also observed while acute laryngitis was noted in one female only. In addition to these changes slight submucosal chronic inflammatory infiltration was evident in approximately half the animals (five males and two females).

In the group 2 animals reparative epithelial hyperplasia was seen in one male and two females while squamous metaplasia and acute laryngitis were observed in one male and three females respectively.

Trachea:

Reparative epithelial hyperplasia was the major change present in the trachea of over half the animals (four males and six females) from group 4. In one male and six females some epithelial degeneration was also seen while mild tracheitis also occurred in three males and three females.

In the group 2 and 3 animals the changes seen were similar, though in most cases less frequent in occurrence, reparative epithelial hyperplasia being present in five males and four females from group 3 and one male and one female from group 2, while mild tracheitis was seen in only four males and one female. Some submucosal chronic inflammatory infiltration was present in one male from group 2 and five males from group 3.

Lung:

At 2.5ppm TDI slight to moderate necrotising bronchitis/bronchiolitis with some bronchial/bronchiolar dilatation, bronchial/bronchiolar debris/plugging and peribronchial/bronchiolar chronic inflammatory infiltration was seen in the majority of animals. Associated with these bronchial/bronchiolar epithelial hyperplasia was observed in all animals; in one male goblet cell differentiation of the hyperplastic epithelium also occurred. In four female rats this was accompanied by a little polyp formation or submucosal obstructive fibrous proliferation. Some squamous metaplasia was present in five males and five females.

Alveolar changes characterised by oedema/fibrin deposition and focal histiocytosis were seen in eight males and seven females from group 4. These changes were accompanied by occasional areas of chronic interstitial infiltration/fibrosis (four males and six females), alveolar/bronchiolar collapse (two males and six females), alveolar epithelialisation (three males and two females), acute alveolitis (five males and three females) and perivascular/ peribronchial neutrophilia (one male and two females).

In the group 3 animals the changes were similar though less severe; slight necrotising bronchitis/bronchiolitis occurring in four males and

five females, bronchial/bronchiolar epithelial hyperplasia was seen in all the animals; this was accompanied by some polyp formation (one male and three females), bronchial/bronchiolar dilatation (one male and two females, bronchial/bronchiolar debris/plugging (five males and four females) and bronchiolar/alveolar collapse (three males and one female.

Oedema/fibrin deposition was seen in the alveoli of one male and two females while focal histiocytosis occurred in half the males and all the females. As in the animals from group 4 these changes were accompanied by chronic interstitial inflammatory infiltration/fibrosis (two females) and acute alveolitis with an associated perivascular neutrophilia (two males and two females).

In the animals from group 2 minimal changes were seen in the lung; these consisted of a little acute bronchiolitis with some associated slight peribronchial chronic inflammatory infiltration (one male) and some focal alveolar histiocytosis (one male and two females).

In addition to the above changes an increase in the peribronchial/ bronchiolar lymphocytic accumulations was seen in six males and five females from group 2 and all the rats in group 3. Associated with these were slight focal areas of chronic bronchitis/bronchiolitis (four males and two females and four males from group 2 and four females from group 3).

Incidental changes:

Cervical lymph node:

Focal minimal acute lymphadenitis was seen in one or two animals from all dose groups exposed to TDI. In one male and two females from group 2 some haemorrhage and erythrophagocytosis was seen in the medulla.

Salivary gland:

A little mild sialoadenitis was seen in the parotid glands of three animals (one male and two females) from group 4 and one male from group 3.

Spleen:

In the animals from group 4 haemopoiesis was minimal in the majority of animals (seven males and eight females), many of these animals having small/shrunken spleens on cross section.

In the rats from group 1 moderate/marked haemopoiesis was seen in three males and four females, the remaining animals exhibiting slight to moderate haemopoietic activity.

Minimal haemopoiesis was also observed in two males and three females from group 3 and in three females from group 2.

Thymus:

Moderate to marked thymic involution was seen in all the males and the majority of females from group 4.

4. DISCUSSION

Previous studies of the toxicity of TDI by inhalation have shown that it acts as a corrosive agent with irritant manifestations proportional to the exposure level, (Zapp, 1957; Duncan et al, 1962; Nilwenhuis, et al, 1965). The organ most affected is the lung where TDI causes tracheobronchitis with sloughing of the superficial epithelium. The results of the study reported here have confirmed the conclusions of the earlier work.

A concentration of 0.1ppm was the target for the low dose group, (group 2) however, due to the difficulties of generating the low levels in the small chambers used, the final average concentration was 0.24ppm. There is no completely satisfactory explanation of why the chamber concentrations were so difficult to maintain, although the air drying equipment was not performing adequately at this time and TDI is very reactive with moisture. Holland and Rooney, 1977, detected a 92% loss of TDI between generation point and chamber at 40% relative humidity, which was

apparently caused by reaction with moisture on the surfaces of the equipment. It is possible that this massive loss at low levels can occur until either the humidity drops or all the available surface becomes covered with 3,3'diisocyanate -4,4'-dimethyl carbanilide as reported by Holland and Rooney, 1977. The loss would then be reduced and a very high concentration of TDI could result in the chamber. It is obvious that with a potential loss of 90% of a generated TDI atmosphere fine control of the generating system to produce the target concentration is at best difficult and, if circumstances conspire against it, almost completely impossible.

The exposure that the lowest concentration group received caused minimal damage and was confined largely to the upper respiratory tract. The

damage was most severe in the nasal passage which is typical of an irritant response. Whilst the average concentration this group received was 0.24ppm, there were large fluctuations as explained earlier and the highest daily average was 0.6ppm which was recorded on two days. These high concentrations could be the cause of the symptoms seen. Some evidence of nasal and eye irritation was noted in the Dow study (Henck et al, 1976) in rats exposed to 0.3ppm, and less severely in rats exposed to 0.1ppm. There was also a decrease in body weight gain in the male rats exposed to 0.3ppm in the Dow study which is evidence of a slight toxic effect. The Dow rats exposed to 0.3ppm average also received a maximum concentration of 0.65ppm. This suggests that while 0.2 -0.3ppm cannot be considered a no effect level, it is impossible to ascribe the effects to such a narrow band of concentrations. There were no abnormalities seen in any of the other parameters or observations made on the rats.

The rats exposed to 0.67ppm (group 3) had more severe damage to the respiratory tract. The nasal passages, larynx, trachea and lungs changes were consistent with the action of an irritant chemical. The response was graded being more severe in the nose and larynx and less severe in the lungs which is consistent with a chemical such as TDI which reacts in the upper respiratory tract so that the effective concentration will be reduced further down the tract, resulting in less severe damage.

There was little or no evidence of other abnormalities in these animals, the damage was confined to the respiratory tract and this was not severe enough to cause secondary systemic toxicity.

The rats which were exposed to 2.83ppm were severely affected. The concentration was large enough to overcome the 'scrubbing' effect of the upper respiratory tract and allow the concentration in the lungs to be high enough to cause bronchitis, bronchiolitis and alveolar changes. Duncan et al (1962) described bronchopneumonia as a complication following single exposures of rats and guinea pigs of up to 10ppm of TDI. Bronchopneumonia was not seen in this study, and though it is conceivable that the difference resulted from multiple exposures in our studies, it is more likely to be a reflection of the pathogen-free status of the Alderley Park rats.

The pulmonary effects were less severe than those reported by Henschler et al, 1962 where 10 exposures at 1ppm were lethal to rats and although adult rats could withstand 24 exposures to 0.5ppm, approximately half the young rats which were exposed died. Most of the deaths were attributed to severe peribronchitis and bronchial pneumonia, probably as a result of a secondary infection as described by Niewenhuis et al, 1965. This underlines the need to use rats free from respiratory infection, in inhalation toxicology so that the complications of a secondary infection do not potentiate a pathological reaction and make interpretation of the results difficult.

The non-invasive lung function test (Hiett, 1972, Swann et al, 1966) only detected the severe changes in the high dose group. However, as the rats were tested before exposure, approximately 18 hours after the previous exposure, the acute effects of TDI would not have been recorded. There would probably have been changes in the lower dose groups if the rats had been tested immediately after exposure, especially on the days when laboured breathing was seen in the group 3 rats and this would have given a guide to the irritancy of the exposures. However, as the background state of the respiratory tract would be measured at this time, the changes in the respiratory tract of groups 2 and 3 were essentially

minor as no functional impairment was seen.

The non-pulmonary changes in the high dose group are probably secondary to serious pulmonary damage. The haematological changes can be associated with attempts to augment the oxygen carrying capacity of the blood by increasing its haemoglobin content by the expulsion of red blood cells from the spleen which would then assume the shrunken appearance as seen by the pathologist. This response is probably a homeostatic mechanism to compensate for the anoxia caused by the pulmonary damage. Both the males and females in group 4 (high dose) had higher AST and ALT levels, which are probably as a result of the stress inflicted by the serious pulmonary damage.

The reduction in urine volume and protein in the group 4 rats could be caused by an effect on the kidney, but as there were no pathological changes seen in the kidney, this is probably a result of decreased food and water intake caused by the rats' clinical condition.

Although a 'no-effect' level was not established in this study, the effects seen in the group 4 rats were minimal and can be attributed to the exposures to high concentrations of TDI on days 7, 12 and 14. If, therefore, 0.24ppm is taken as a minimal effect level and a safety factor of ten is applied a hygiene standard of 0.024ppm would be applied. This is no different, in practial terms, to the present ceilng limit TLV for TDI of 0.02ppm (NIOSH, 1978), which is designed to protect against irritation of the respiratory tract as well as sensitisation, and is above the time weighted average of .005ppm. Thus this study has demonstrated that the TLV is justified on the grounds of irritancy alone without taking into account sensitisation.

5. CONCLUSION

TDI has been confirmed by this experiment as corrosive to the respiratory tract. The severity of respiratory tract damage

varied with the exposure concentration. Severe damage involving the whole of the respiratory tract occurred in the rats exposed to 2.83ppm. Exposure to 0.67ppm caused less severe damage, and minimal damage confined to the upper respiratory tract was seen following exposure to 0.24ppm.

JED/CG/JO/SJ/GW
19.12.79

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TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

TABLE 1

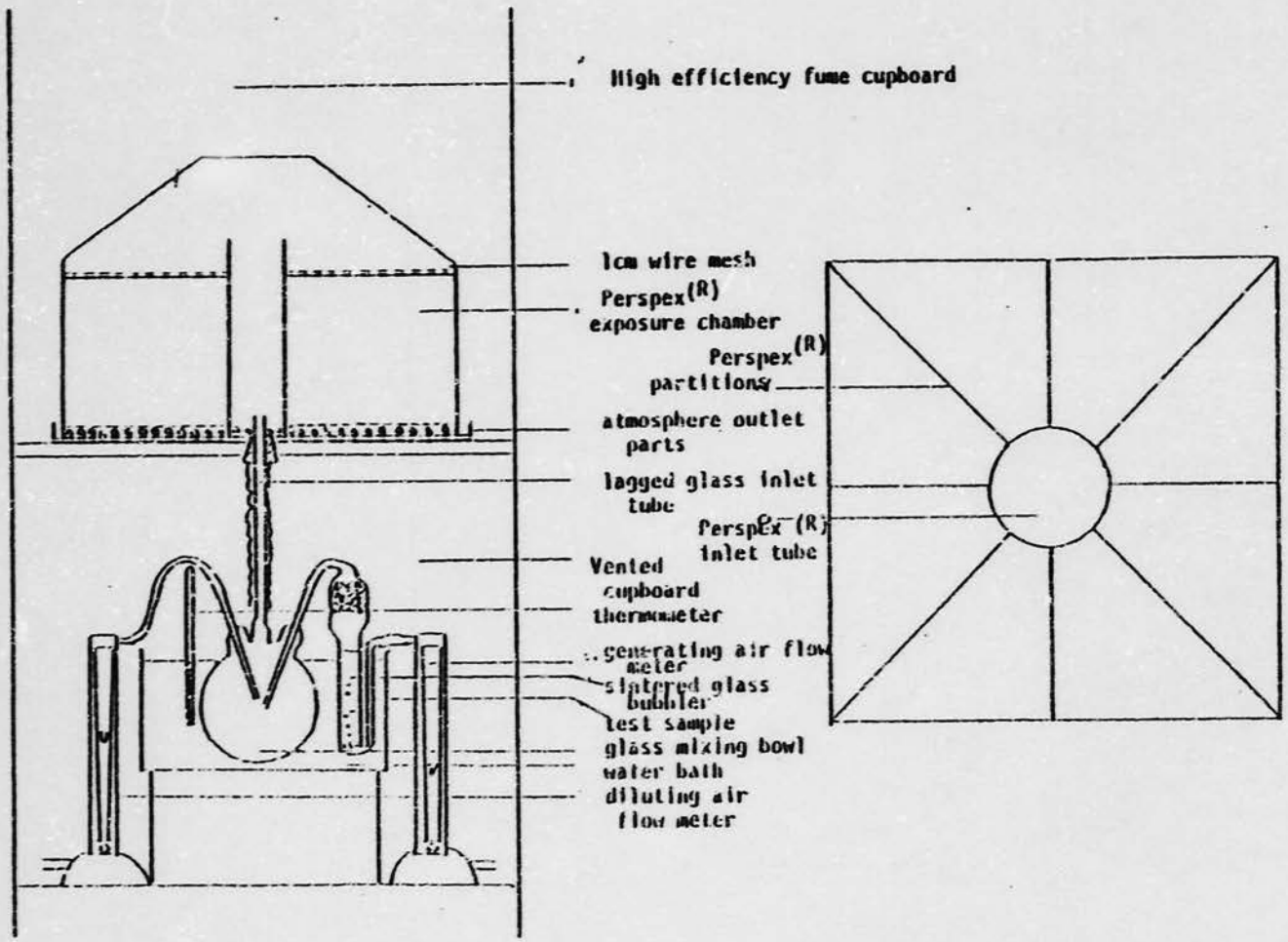
FLOW CHART OF TOLYLENE DI-ISOCYANATE PROTOCOL

Day	Pre	Pre	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Batch I	W	W	W	W			W	W		W				W		W		W			W		W			
								LF							LF							LF				
	LF		FW					FW							FW							FW				
			E	E			E	E	E	E	E			E	E	E	E	E			E	E	E	P.M.		
Day		Pre	Pre	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Batch II		W	W	W	W			W	W		W				W		W				W	W		W		
		LF		E	E		E	E	E	E	E			E	E	E	E	E			E	E	E	E	P.M.	
				FW					LF							LF							LF			
									FW							FW							FW			
8/77	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S

Key: W = Weighed LF = Lung Function FW = Food and Water Intake E = Exposed
P.M. = Post Mortem Examination

TDI SUB-ACUTE INHALATION STUDY.

FIGURE 1 : GENERATION AND EXPOSURE SYSTEM FOR TDI

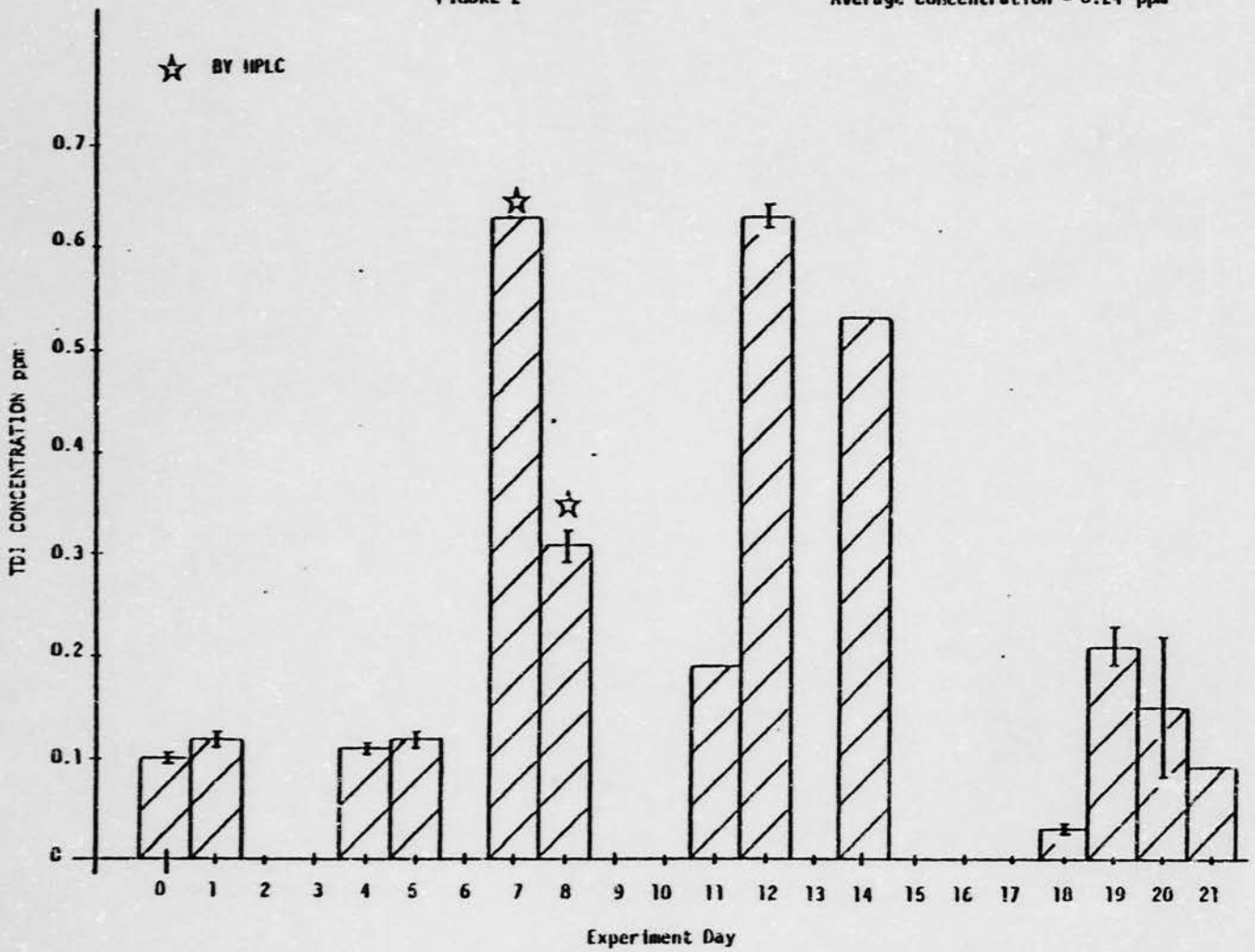


TDI SUB-ACUTE INHALATION : TARGET CONCENTRATION 0.1 ppm

DAILY MEAN AND STANDARD ERROR OF TDI CONCENTRATION MEASURED BY HARCALI

FIGURE 2

Average Concentration = 0.24 ppm



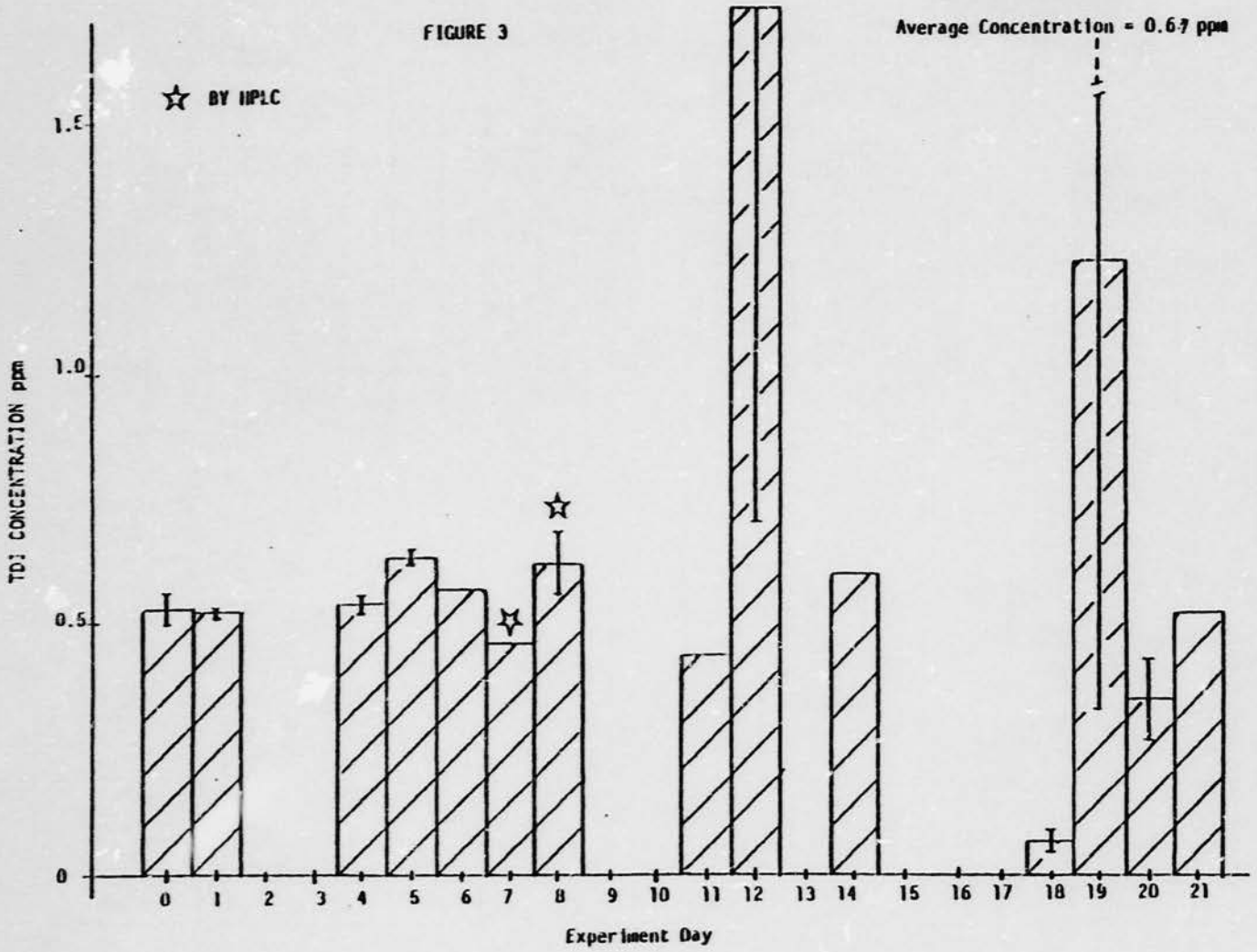
TDI SUB-ACUTE INHALATION : TARGET CONCENTRATION 0.5 ppm

DAILY MEAN AND STANDARD ERROR OF TDI CONCENTRATIONS

MEASURED BY MARCALI

FIGURE 3

Average Concentration = 0.67 ppm



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TDI SUB-ACUTE INHALATION : TARGET CONCENTRATION 2.5 ppm

DAILY MEAN AND STANDARD ERROR OF TDI CONCENTRATION MEASURED BY MARCALI

FIGURE 4

Average Concentration = 2.83 ppm

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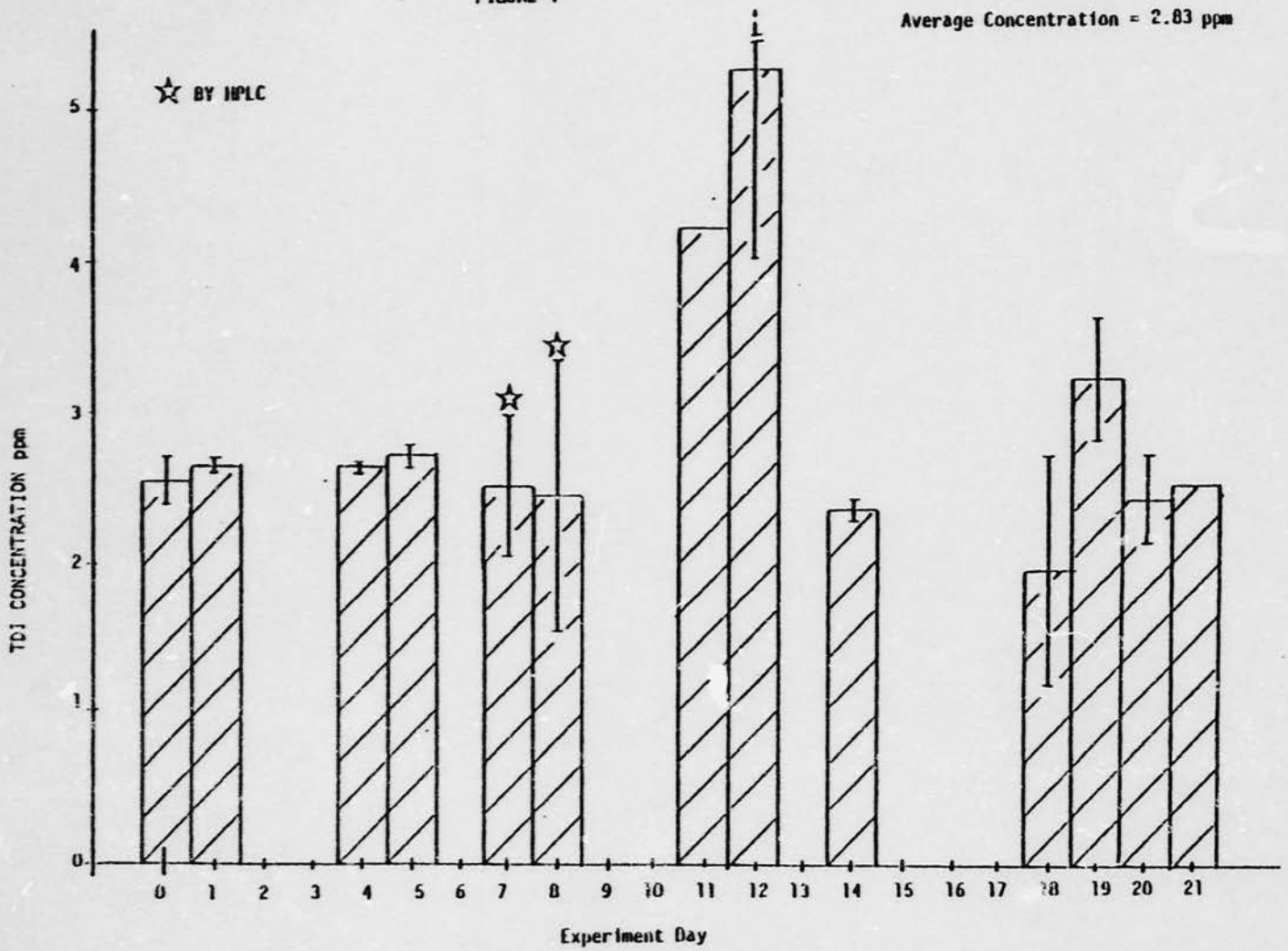
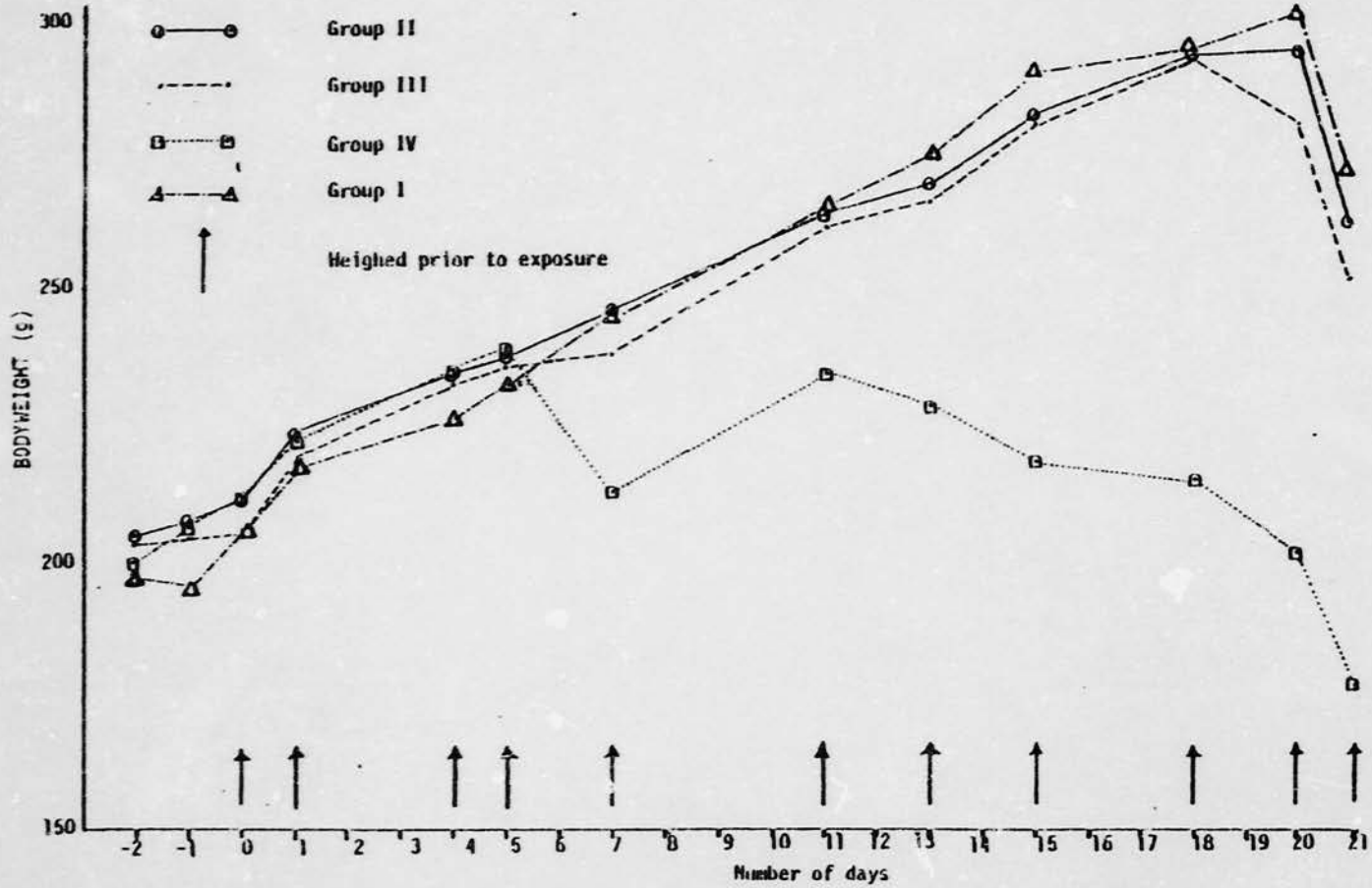


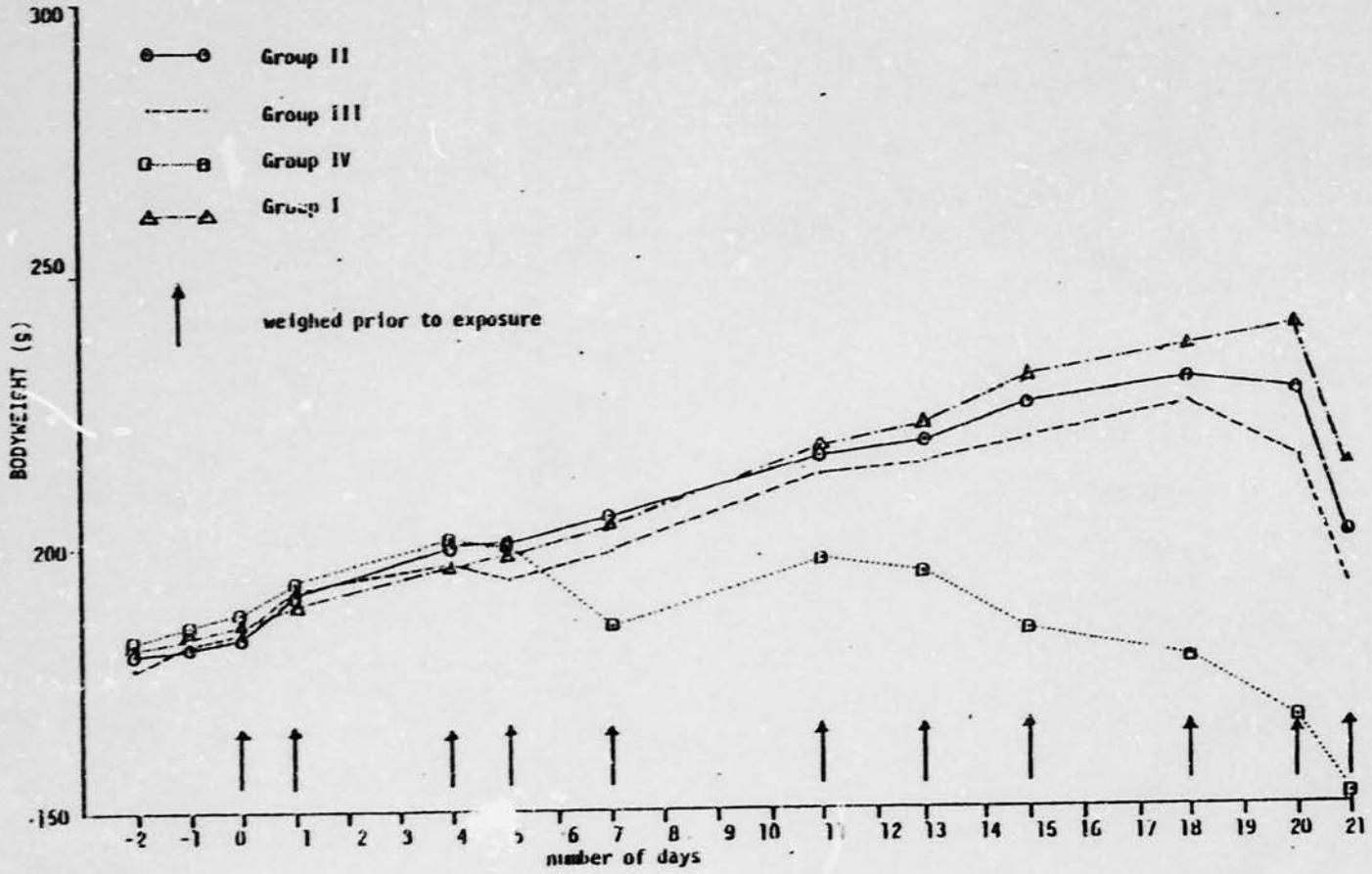
TDI SUB-ACUTE INHALATION STUDY

FIGURE 5 : TDI BODYWEIGHTS (MALE)



TDI SUB-ACUTE INHALATION STUDY

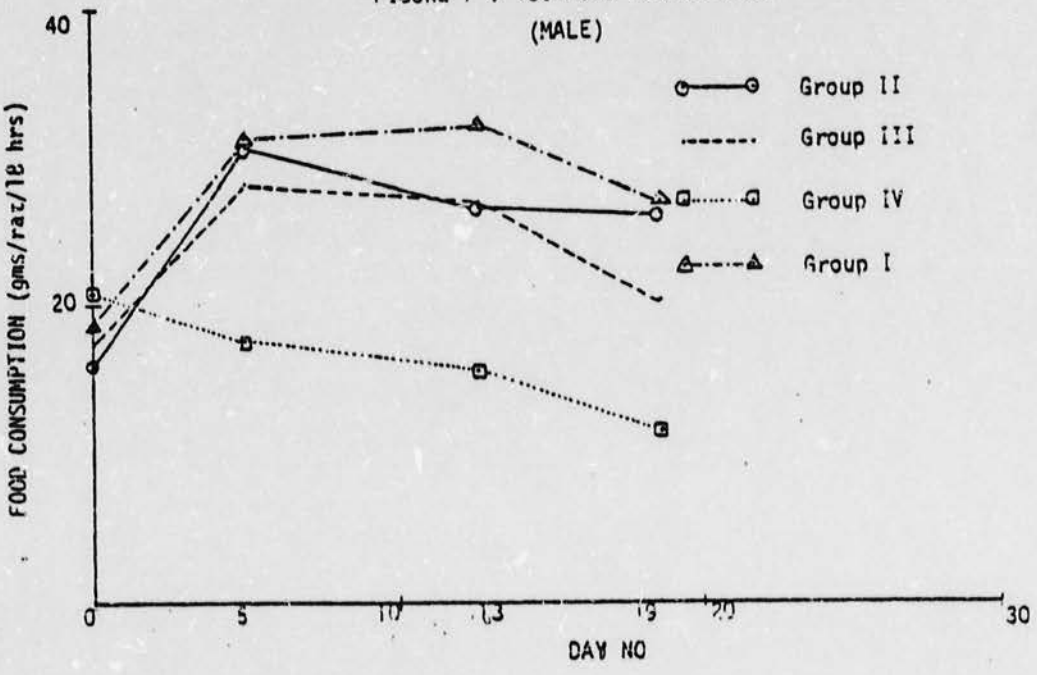
FIGURE 6 : TDI BODYWEIGHTS (FEMALE)



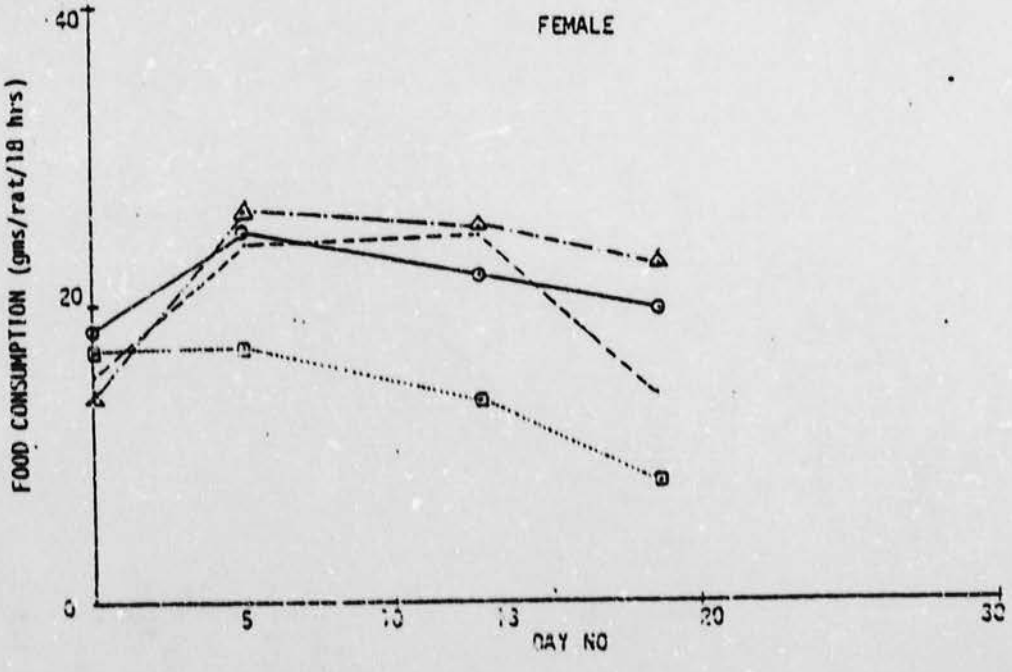
TDI SUB-ACUTE INHALATION STUDY

FIGURE 7 : TDI FOOD CONSUMPTION

(MALE)



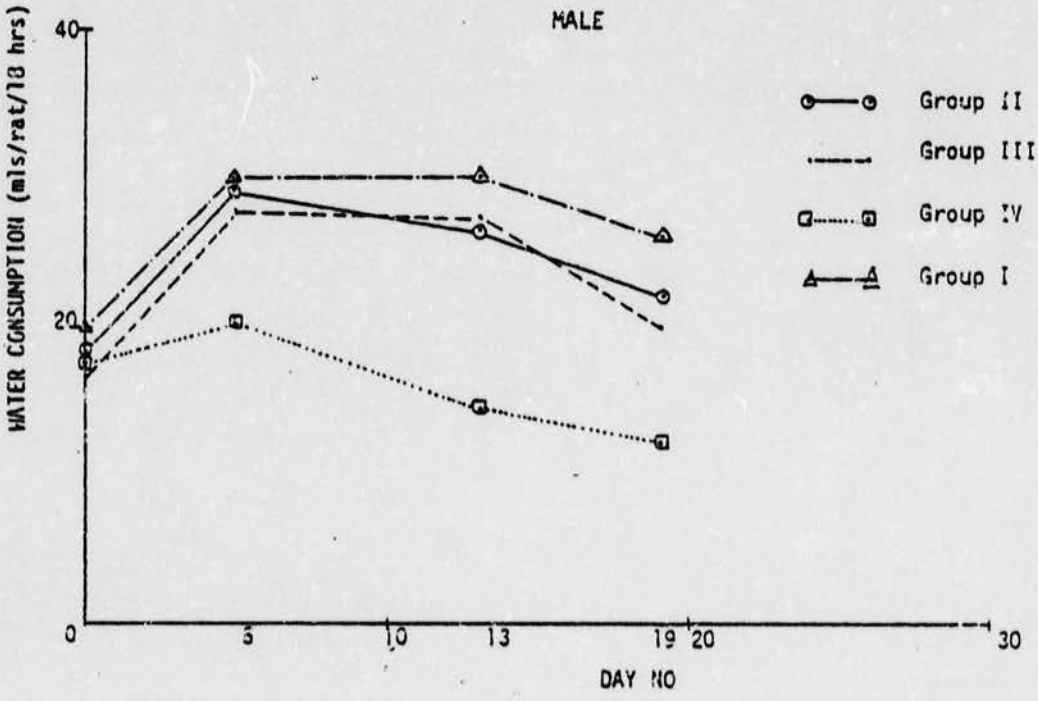
FEMALE



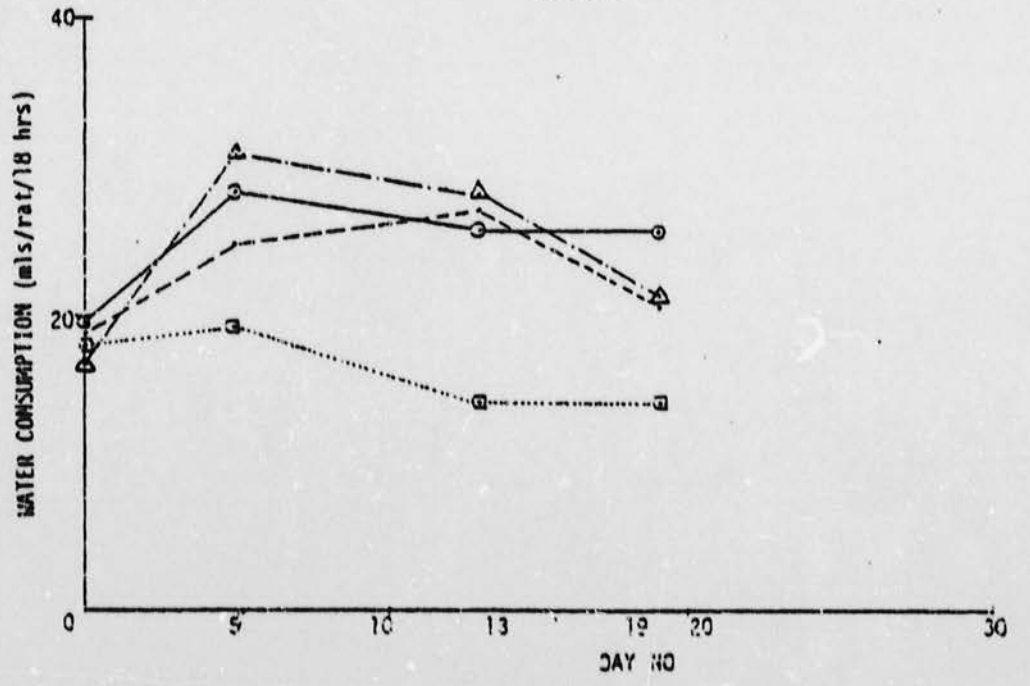
TDI SUB-ACUTE INHALATION STUDY

FIGURE 8: TDI WATER CONSUMPTION

MALE



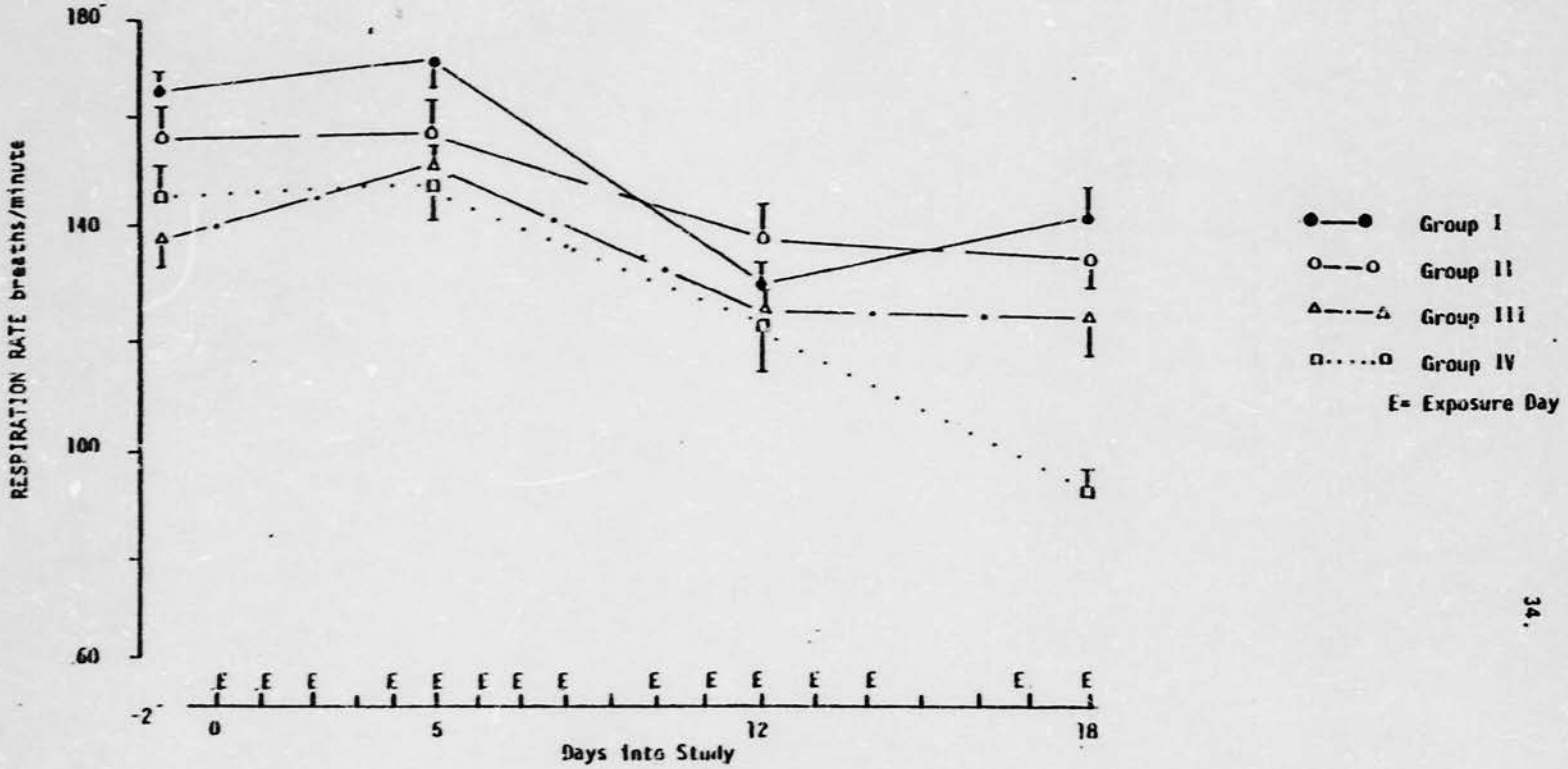
FEMALES



TDI SUB-ACUTE STUDY : LUNG FUNCTION PARAMETERS : RESPIRATION RATE

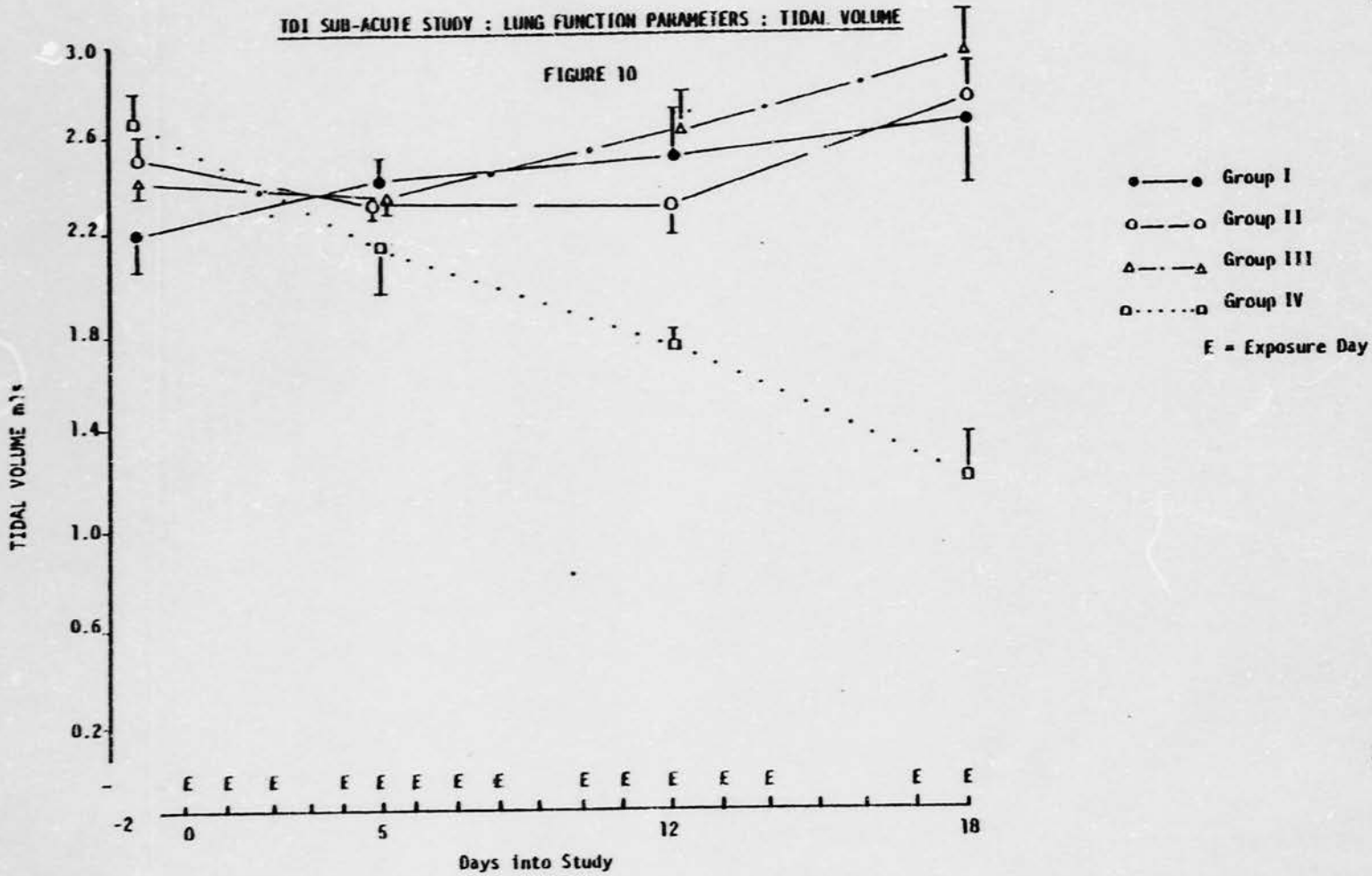
FIGURE 9

MALES AND FEMALES



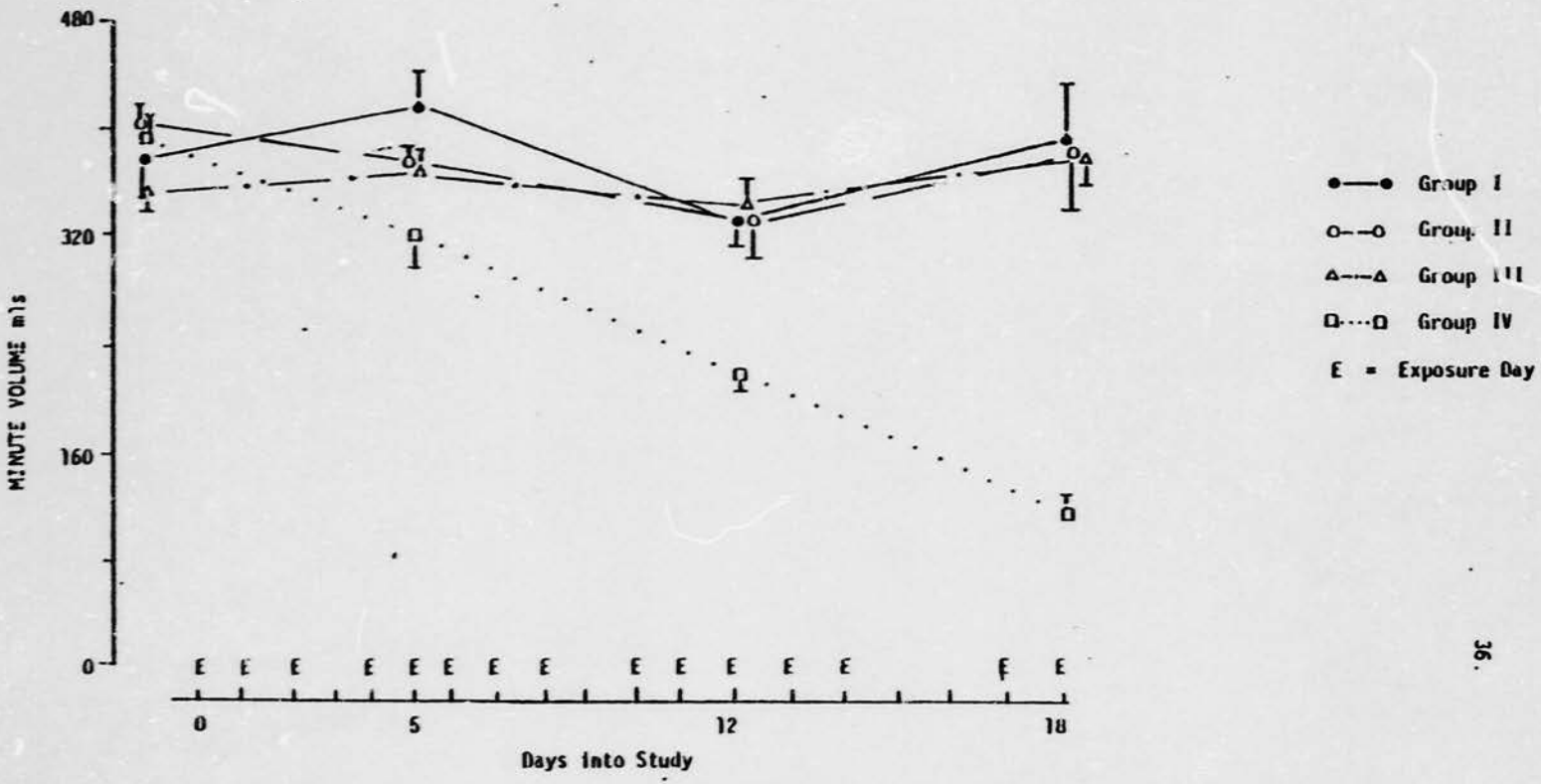
TDI SUB-ACUTE STUDY : LUNG FUNCTION PARAMETERS : TIDAL VOLUME

FIGURE 10



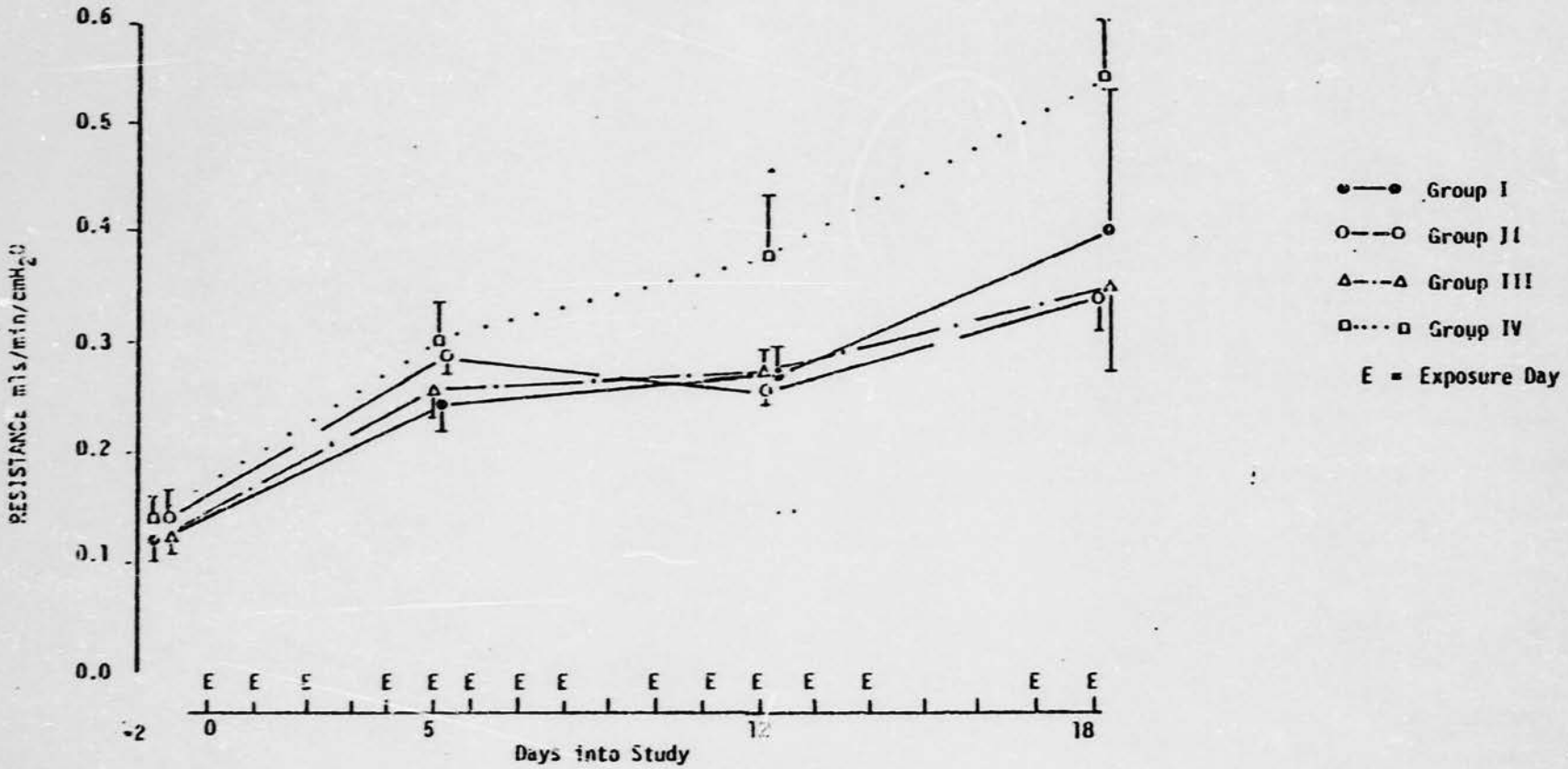
TDI SUB-ACUTE STUDY : LUNG FUNCTION PARAMETERS : MINUTE VOLUME

FIGURE 11



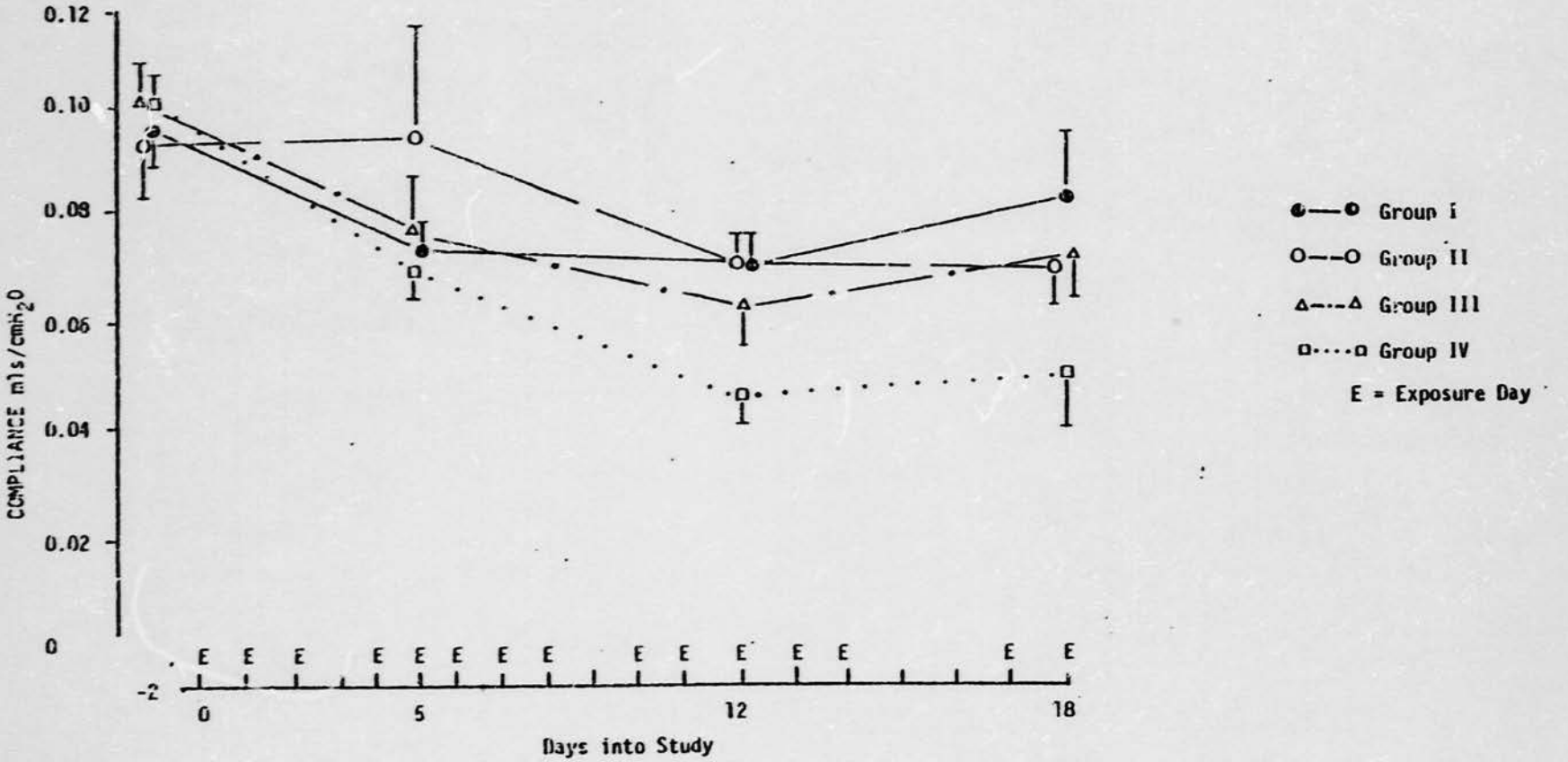
TDI SUB-ACUTE STUDY : LUNG FUNCTION PARAMETERS : RESISTANCE

FIGURE 12

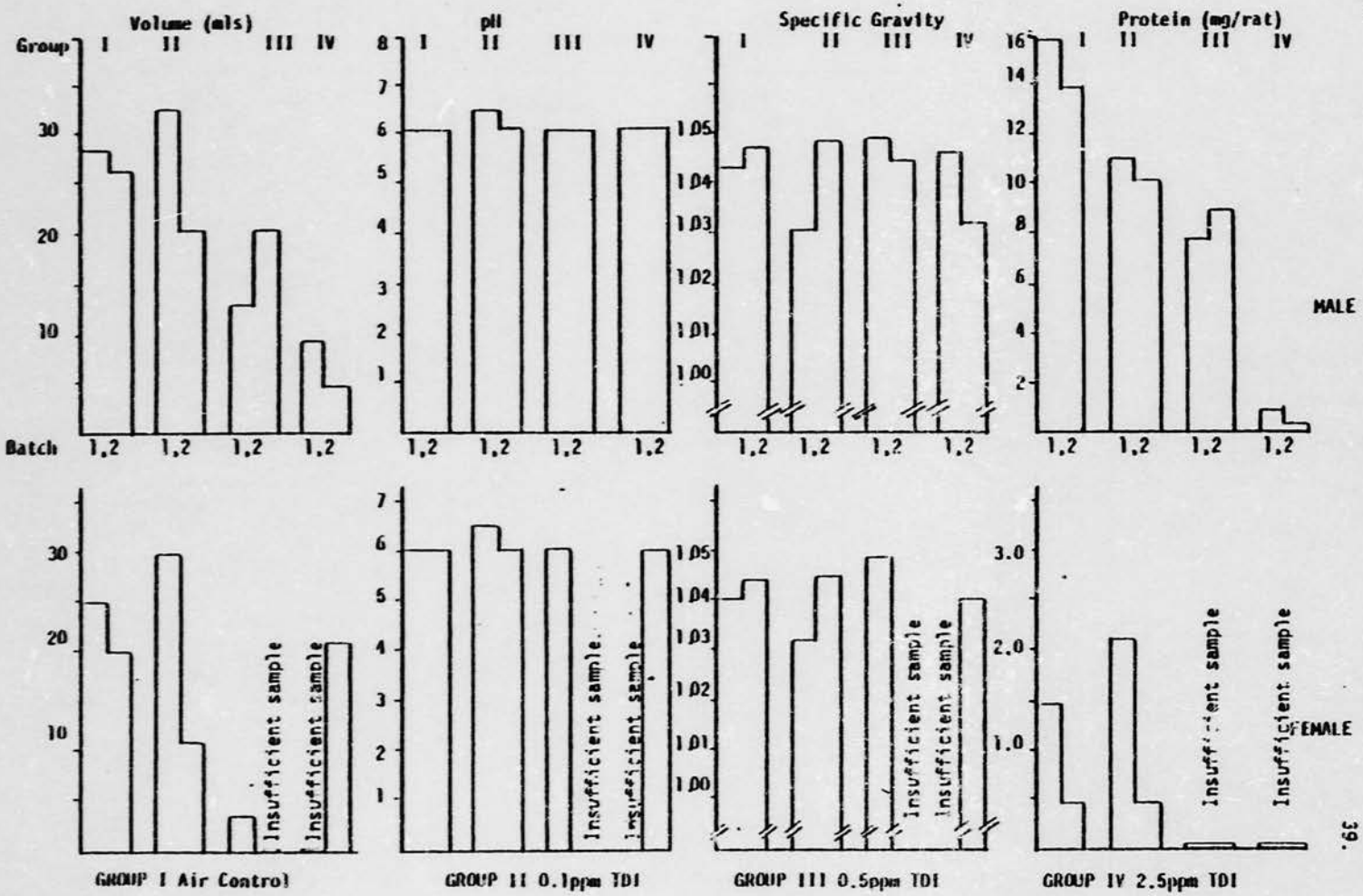


TDI SUB-ACUTE STUDY : LUNG FUNCTION PARAMETERS : COMPLIANCE

FIGURE 13



TDI SUB-ACUTE INHALATION STUDY
FIGURE 14: TDI URINE ANALYSIS



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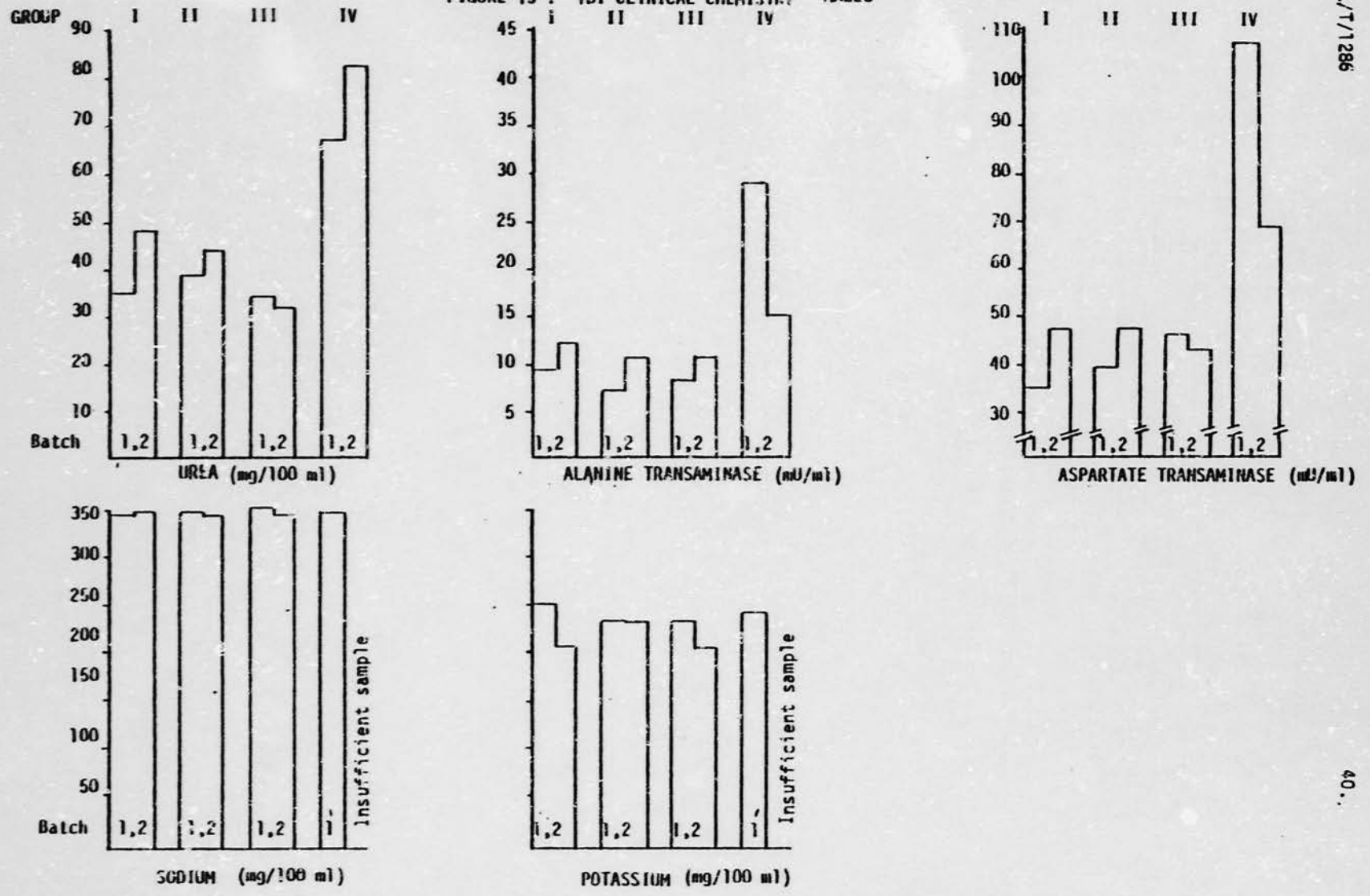
TDI SUB-ACUTE INHALATION STUDY

FIGURE 15 : TDI CLINICAL CHEMISTRY - MALES



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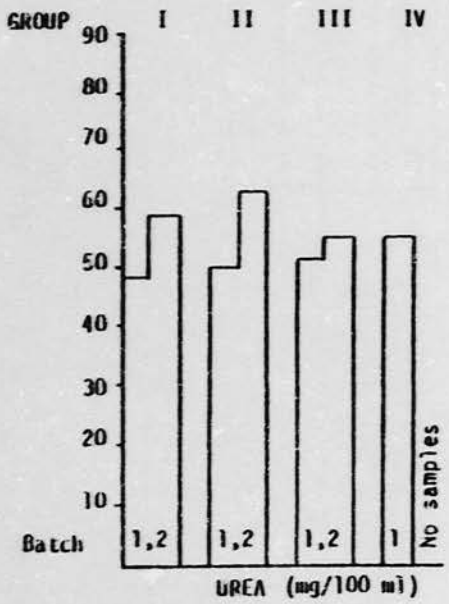
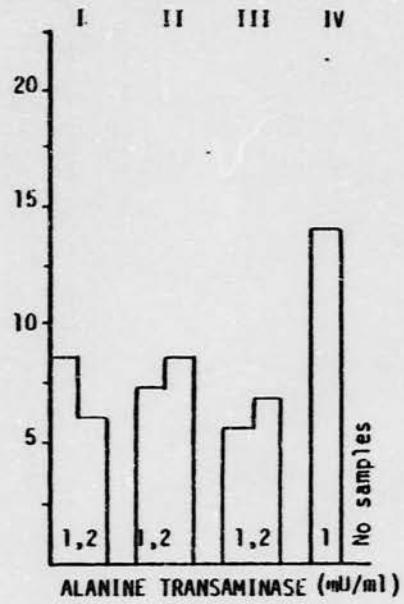
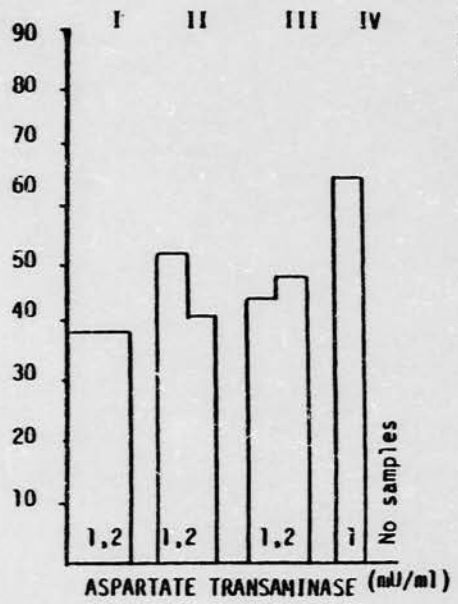
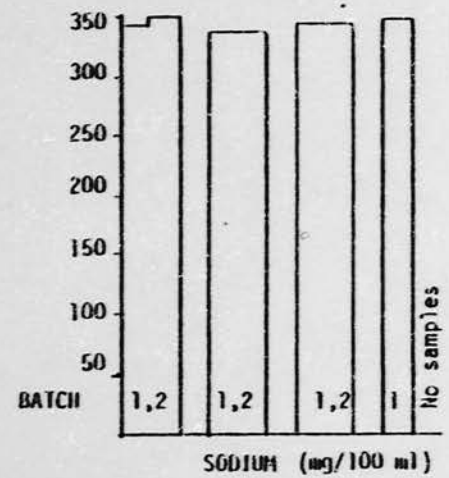
TDI SUB-ACUTE INHALATION STUDY

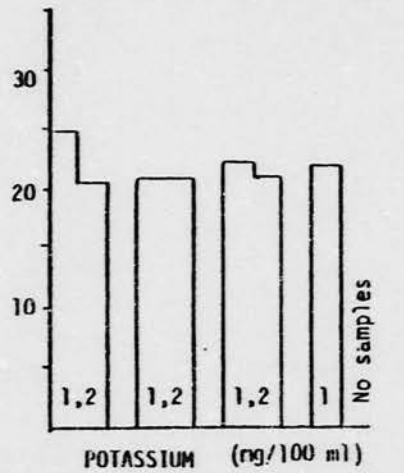
FIGURE 16 : TDI CLINICAL CHEMISTRY - FEMALES











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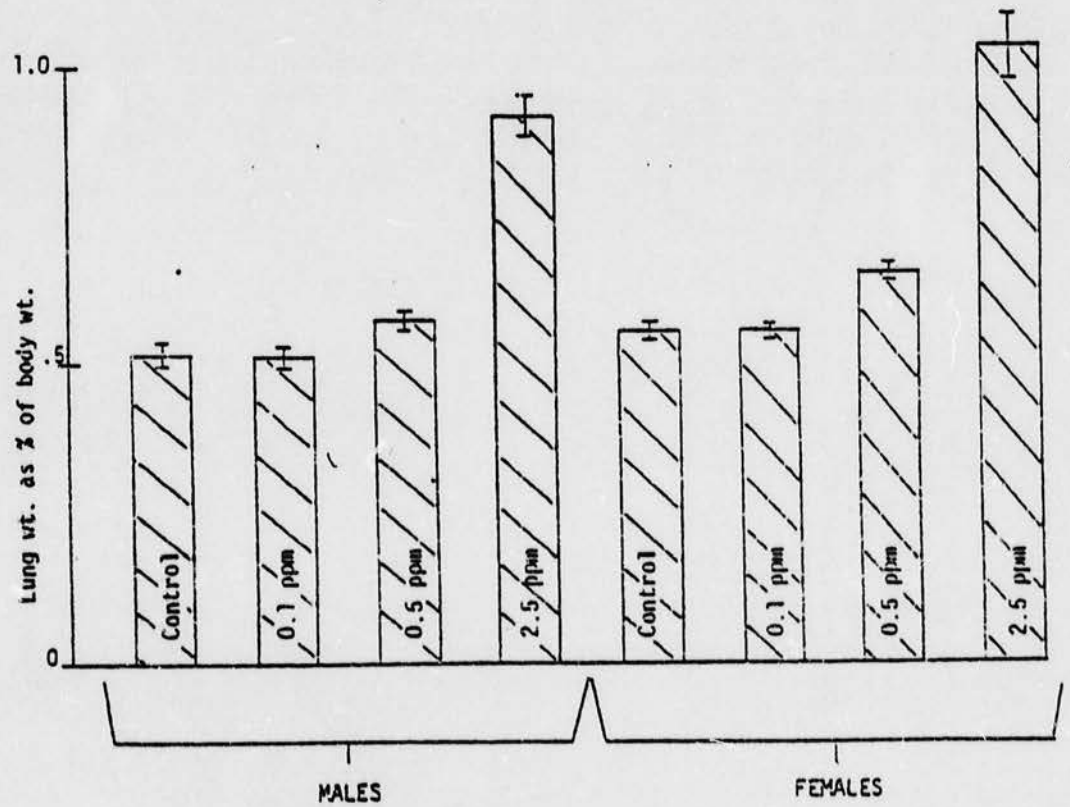
TDI SUB-ACUTE INHALATION STUDY

TDI LUNG WEIGHTS

FIGURE 17



TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 1

TDI ATMOSPHERE ANALYSIS TABLE 1

Date	Expt day	Nominal concentration		
		2.5	0.5	0.1
4/8	0	2.57 2.59 1.47 2.53 3.08 ±0.16 2.59 2.72 2.59	0.51 0.49 0.64 0.53 0.52 ±0.03 0.64 0.49 0.43	0.107 0.110 0.103 0.12 ±0.005 0.09 0.092 0.089 0.11
5/8	1	2.57 2.541 2.63 2.611 ±0.04 2.68 2.75	0.512 0.511 0.52 0.533 ±0.01 0.524 0.54	0.105 0.123 0.116 0.106 ±0.005 0.115 0.133
8/8	4	2.81 2.48 2.61 2.59 ±0.05 2.58 2.58	0.516 0.475 0.54 0.59 ±0.02 0.57 0.56	0.108 0.098 0.111 0.12 ±0.004 0.12 0.11

* by HPLC otherwise by Marcali values shown are mean ± standard errors

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 1 - continued

TDI ATMOSPHERE ANALYSIS TABLE 2

Date	Expt day	Nominal concentration		
		2.5ppm X±SEM	0.5ppm X±SEM	0.1ppm X±SEM
9/8	5	2.66 2.56 2.71 2.82 ±0.04 2.68	0.62 0.62 0.63 0.66 ±0.01 0.62	0.106 0.13 0.122 0.12 ±0.006 0.13
10/8	6	2.33 2.33	0.51 0.51	0.11 0.11
11/8	7	3.09 2.52 1.613 ±0.46 2.86	0.461* 0.463	0.631* 0.631
12/8	8	 3.42* 3.33 1.916* ±0.79 4.65*	0.59* 0.67* 0.624 0.47* 0.77* ±0.06	0.344* 0.278* 0.307 0.306* ±0.014 0.298*
15/8	11	4.24 4.24	0.4[illegible] 0.44	0.19 0.19
16/8	12	4.00 5.26 6.52 ±1.26	0.7 1.73 2.76 ±1.[illegible]3	0.62 0.63 0.63 ±0.005

* by HPLC otherwise by Marcali values shown are mean ± standard errors.

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 1 - continued

TDI ATMOSPHERE ANALYSIS TABLE 3

Date	Expt day	Nominal concentration		
		2.5ppm X±SEM	0.5ppm X±SEM	0.1ppm X±SEM
18/8	14	2.28 2.34 2.39 ±0.06	0.6 0.6	0.53 0.53
22/8	18	0.86 0.61 1.94 2.43 ±0.76 3.86	0.08 0.05 0.065 ±0.02	0.04 0.03 0.030 0.02 ±0.004 0.028
23/8	19	3.67 3.19 3.5 ±0.40 2.4	3.0 1.22 0.41 ±0.89 0.262	0.18 0.207 0.19 ±0.022 0.25
24/8	20	2.21 2.00 2.39 3.3 ±0.31 2.04	0.48 0.21 0.35 0.37 ±0.08	0.10 0.05 0.15 0.06 ±0.068 0.19
25/8	21	2.51 2.51	0.52 0.52	0.09 0.09
Overall Mean SD SE		2.83 ±0.88 ±0.235	0.67 ± 0.362 ± 0.097	0.238 ±0.206 ±0.005

* by HPLC otherwise by Marcali values shown are mean ± standard errors.

TOLYLENE DI-ISOCYANATE THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 2 TABLE 1 MR0001

BODYWEIGHTS - GROUP I MALE

Batch 1 Actual day				0	1	4	5	6	7	8	11	12	13	14	15	18	19	20	21
Exposure day		Pre	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	PM
Cage 1	1	203	201	204	205	205	224	-	243	-	265	-	270	-	284	294	-	293	283
	2	187	176	196	198	212	219	-	231	-	247	-	253	-	260	275	-	279	252
	3	187	183	192	190	216	215	-	228	-	247	-	261	-	276	290	-	298	268
	4	214	190	217	222	233	240	-	249	-	257	-	282	-	293	302	-	305	278
Average		197.75	187.50	202.25	203.75	216.50	224.50		237.75		254.00		266.50		275.75	290.25		293.75	265.25
Standard deviation		13.20	10.66	11.00	13.62	11.90	10.97		9.91		8.72		12.45		11.09	11.32		11.00	10.80
Batch 2 Actual day				0	3	4	5	6	7	10	11	12	13	14	17	18	19	20	PM
Cage 2	5	200	207	216	242	254	257	-	274	-	296	-	313	320	324	320	-	340	303
	6	184	189	195	214	220	224	-	234	-	254	-	263	265	286	283	-	285	265
	7	211	220	223	242	246	245	-	262	-	282	-	289	291	305	308	-	313	282
	8	184	196	201	224	227	232	-	247	-	262	-	275	272	295	290	-	297	267
Average		194.75	203.00	208.75	230.50	236.75	239.50		254.25		273.50		285.00	287	302.5	300.25		308.75	279.25
Standard deviation		13.20	13.54	12.97	13.90	15.90	14.53		17.44		19.07		21.48	24.59	16.30	16.66		23.78	17.55
Total average		196.25	195.25	205.50	217.13	236.63	232.00		246.00		263.75		275.75		289.13	295.25		301.25	272.75
Total standard deviation		12.33	14.00	11.67	19.15	16.92	14.36		15.82		17.24		19.02		19.26	14.33		18.93	15.43

TOLYLENE DI-ISOCYANATE THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 2 TABLE 2 HR0001

BODYWEIGHTS - GROUP 1 FEMALE

Batch 1 actual day				0	1	4	5	6	7	8	11	12	13	14	15	18	19	20	21
Exposure day			Pre	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	PM
Cage 3	9		181	178	176	182	187	190	-	199	-	208	-	207	-	215	224	-	223	206
	10		174	170	169	168	182	186	-	197	-	200	-	200	-	210	215	-	220	202
	11		182	180	182	184	200	202	-	208	-	225	-	225	-	240	235	-	239	211
	12		180	193	185	187	201	201	-	203	-	219	-	228	-	220	246	-	247	220
Average			179.25	177.75	178.00	180.25	192.50	194.75		201.75		213.00		215.00		221.75	230.00		232.25	209.75
Standard deviation			3.59	5.56	7.07	8.42	9.47	7.97		4.86		11.17		13.64		13.15	13.44		12.89	7.76
Batch 2 actual day					0	3	4	5	6	7	10	11	12	13	14	17	18	19	20	PM
Cage 4	13		193	196	197	210	211	212	-	222	-	230	-	238	239	243	247	-	254	227
	14		179	186	194	199	203	200	-	210	-	228	-	240	245	257	258	-	258	233
	15		184	181	186	193	197	197	-	203	-	215	-	225	226	233	238	-	246	211
	16		173	182	184	189	194	194	-	196	-	211	-	210	219	224	220	-	227	202
Average			182.25	187.00	190.25	197.75	201.25	200.75		207.75		221.00		228.25	232.25	239.25	240.75		246.25	218.25
Standard deviation			8.46	6.22	6.24	9.14	7.50	7.89		11.09		9.42		13.87	11.87	14.15	16.07		13.77	14.27
Total average			180.75	182.38	184.13	189.00	196.88	197.75		204.75		217.00		221.63		230.75	235.38		239.25	214.00
Total standard deviation			6.23	7.37	9.00	12.40	9.19	8.01		8.55		10.47		14.57		15.89	14.87		14.44	11.56

TOLYLENE DI-ISOCYANATE THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 2 TABLE 3 HR0001

BODYWEIGHTS - GROUP II MALE

Batch 1 Actual day				0	1	4	5	6	7	8	11	12	13	14	15	18	19	20	21
Exposure day		Pre	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	PM
Cage 5	17	210	214	217	221	232	243	-	253	-	271	-	276	-	286	307	-	314	281
	18	213	213	221	223	248	247	-	263	-	274	-	280	-	295	309	-	307	274
	19	208	209	215	217	240	245	-	252	-	280	-	287	-	291	304	-	314	280
	20	217	212	217	218	237	248	-	250	-	260	-	256	-	265	276	-	275	245
Average		212.00	212.00	217.50	219.75	239.25	245.75		254.50		271.25		274.75		284.25	299.00		302.50	270.00
Standard deviation		3.92	2.16	2.52	2.75	6.70	2.22		5.80		8.38		13.30		13.35	15.47		18.63	16.95
Batch 2 Actual day				0	3	4	5	6	7	10	11	12	13	14	17	18	19	20	PM
Cage 6	21	205	210	212	238	240	237	-	247	-	263	-	267	-	277	283	-	285	255
	22	183	182	184	210	225	218	-	233	-	253	-	257	-	270	280	-	290	250
	23	200	206	210	230	231	234	-	240	-	264	-	272	-	290	295	-	290	261
	24	201	204	208	223	233	229	-	233	-	243	-	258	-	274	283	-	286	255
Average		197.25	200.50	203.50	225.25	232.25	229.50		238.25		255.75		263.50		277.75	285.25		285.25	255.25
Standard deviation		9.74	12.58	13.10	11.87	6.18	8.35		6.70		9.84		7.23		8.66	6.65		4.11	4.50
Total average		204.63	206.25	210.50	222.50	235.75	237.63		246.38		263.50		269.13		281.00	292.13		293.88	262.63
Total standard deviation		10.46	10.38	11.50	8.50	7.05	10.36		10.45		11.84		11.59		10.98	13.25		15.52	13.93

TOLYLENE DI-ISOCYANATE THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 2 TABLE 4 MR0001

BODYWEIGHTS - GROUP II FEMALE

Batch 1 Actual day				0	1	4	5	6	7	8	11	12	13	14	15	18	19	20	21
Exposure day		Pre	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	PM
Cage 7	25	180	179	179	182	202	202	-	204	-	218	-	225	-	220	226	-	230	203
	26	172	164	166	170	187	187	-	191	-	197	-	206	-	208	216	-	214	192
	27	190	189	193	184	209	207	-	220	-	230	-	234	-	248	248	-	240	213
	28	187	188	188	190	200	200	-	200	-	210	-	210	-	205	218	-	207	190
Average		182.25	180.00	181.50	181.50	199.50	199.00		203.75		213.75		218.75		220.25	227.00		222.75	199.50
Standard deviation		8.02	11.58	11.84	8.39	9.18	8.52		12.12		13.87		13.05		19.60	14.65		15.00	10.66
Batch 2 Actual day				0	3	4	5	6	7	10	11	12	13	14	17	18	19	20	PM
Cage 8	29	186	192	195	212	220	215	-	224	-	231	-	238	-	250	245	-	250	212
	30	176	181	183	200	198	203	-	205	-	219	-	217	-	235	237	-	229	204
	31	177	175	177	191	193	195	-	200	-	215	-	210	-	226	229	-	232	208
	32	171	176	178	190	195	195	-	200	-	210	-	204	-	211	214	-	224	191
Average		177.50	181.00	183.25	198.25	201.50	202.00		207.25		218.75		217.25		230.50	231.25		233.75	203.75
Standard deviation		6.24	7.79	8.26	10.21	12.50	9.45		11.41		8.96		14.82		16.34	13.23		11.32	9.10
Total average		179.88	180.50	182.38	189.88	200.50	200.50		205.50		216.25		218.00		225.38	229.13		228.25	201.60
Total standard deviation		7.12	9.15	9.50	12.40	10.[illegible]	8.49		11.06		11.13		12.95		17.58	13.12		13.64	9.46

TOLYLENE DI-ISOCYANATE THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 2 TABLE 5 AROCO1

BODYWEIGHTS - GROUP III MALE

Batch 1 Actual day				0	1	4	5	6	7	8	11	12	13	14	15	18	19	20	21
Exposure day		Pre	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	PM
Cage 9	33	200	199	203	202	230	231	-	237	-	257	-	263	-	256	286	-	273	244
	34	203	197	200	201	221	235	-	236	-	262	-	261	-	270	288	-	285	253
	35	193	194	198	203	224	232	-	237	-	264	-	265	-	266	285	-	280	253
	36	209	207	206	211	239	247	-	253	-	280	-	286	-	295	316	-	306	272
Average		201.25	199.25	201.00	204.25	228.50	236.25		240.75		265.75		274.25		293.75	293.75		286.00	355.50
Standard deviation		6.65	5.56	3.46	4.57	7.94	7.37		8.18		9.95		11.62		13.96	14.89		14.21	11.79
Batch 2 Actual day				0	3	4	5	6	7	10	11	12	13	14	17	18	19	20	PM
Cage 10	37	201	206	207	230	235	233	-	228	-	253	-	163	-	283	285	-	264	241
	38	200	205	205	220	222	219	-	227	-	246	-	248	-	270	276	-	265	239
	39	199	202	206	226	235	233	-	230	-	245	-	257	-	275	277	-	255	239
	40	215	215	217	243	249	247	-	250	-	281	-	284	-	320	323	-	314	279
Average		203.75	207.00	208.75	230.25	233.25	233.00		233.75		256.25		263.00		287.00	290.25		274.50	249.50
Standard deviation		7.54	5.60	5.56	9.54	11.03	11.43		10.90		16.08		15.30		22.64	22.20		26.71	19.69
Total average		202.50	203.13	204.88	217.25	231.88	234.63		237.75		261.00		265.88		290.63	292.00		280.25	252.50
Total standard deviation		6.72	6.62	5.96	15.53	9.60	9.07		9.68		13.79		12.94		18.70	17.60		20.74	15.36

TOLYLENE DI-ISOCYANATE THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 2 TABLE 6 MN0001

BODYWEIGHTS - GROUP III FEMALE

Batch 1 Actual day				C	1	4	5	6	7	8	11	12	13	14	15	18	19	20	21
Exposure day		Pre	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	PM
Cage 11	41	193	190	199	196	210	205	-	210	-	229	-	220	-	227	237	-	226	203
	42	180	178	182	184	194	195	-	200	-	210	-	210	-	215	225	-	212	193
	43	172	174	178	177	192	192	-	194	-	206	-	206	-	208	213	-	207	183
	44	198	196	204	204	226	219	-	231	-	242	-	240	-	250	260	-	252	224
Average		185.75	184.50	190.75	190.25	205.50	202.75		208.75		221.75		219.00		225.00	233.75		224.25	200.75
Standard deviation		11.90	10.25	12.69	12.07	15.86	12.18		16.24		16.82		15.19		18.42	20.06		20.17	17.52
Batch 2 Actual day				0	3	4	5	6	7	10	11	12	13	14	17	18	19	20	PM
Cage 12	45	155	165	168	171	176	173	-	174	-	186	-	192	-	197	197	-	194	172
	46	167	169	172	183	186	183	-	180	-	197	-	209	-	214	219	-	194	176
	47	167	173	174	196	191	190	-	192	-	209	-	212	-	210	222	-	214	189
	48	189	197	198	213	201	202	-	210	-	227	-	224	-	227	230	-	218	200
Average		169.50	176.00	176.00	190.75	188.50	187.00		189.00		204.75		209.25		212.00	217.00		205.00	184.25
Standard deviation		14.18	14.33	13.56	16.01	10.41	12.19		15.87		17.56		13.20		12.36	14.12		12.81	12.76
Total average		177.63	180.25	184.38	190.50	197.00	194.88		198.88		213.25		214.13		218.50	225.38		214.63	192.50
Total standard deviation		14.91	12.42	13.94	14.19	15.39	14.08		18.23		18.33		14.17		16.10	18.38		18.72	16.71

TOLYLENE DI-ISOCYANATE THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 2 TABLE 7 HRG001

BODYWEIGHTS - GROUP IV MALE

Batch 1 Actual day				0	1	4	5	6	7	8	11	12	13	14	15	18	19	20	21
Exposure day		Pre	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	PM
Cage 13	49	200	202	212	215	227	239	-	217	-	240	-	231	-	218	230	-	213	187
	50	205	200	210	211	227	236	-	220	-	224	-	210	-	136	207	-	180	157
	51	206	206	214	210	230	236	-	215	-	225	-	226	-	289	205	-	173	156
	52	190	182	190	192	220	225	-	206	-	221	-	220	-	220	231	-	207	185
Average		197.75	197.50	206.50	207.00	226.00	234.00		214.50		227.50		221.75		203.25	218.75		193.25	171.25
Standard deviation		12.12	10.63	11.12	10.22	4.24	6.16		6.03		8.50		9.03		18.25	14.17		19.70	17.01
Batch 2 Actual day				0	3	4	5	6	7	10	11	12	13	14	17	18	19	20	PM
Cage 14	53	207	222	225	240	248	247	-	216	-	246	-	237	-	206	197	-	0	0
	54	202	207	210	229	237	239	-	205	-	242	-	240	-	255	230	-	223	196
	55	202	210	211	234	239	244	-	205	-	230	-	220	-	237	204	-	205	172
	56	198	210	213	234	243	213	-	207	-	240	-	237	-	233	210	-	207	180
Average		202.25	212.25	214.75	234.25	241.75	243.25		208.25		239.50		233.50		232.75	210.25		211.67	182.67
Standard deviation		3.69	6.65	6.95	4.50	4.86	3.30		5.25		6.21		9.11		20.24	14.20		9.87	12.22
Total Average		200.00	204.88	210.63	220.63	233.88	238.63		211.38		233.50		227.63		218.00	214.25		201.14	176.14
Total Standard deviation		2.64	11.32	9.65	16.30	9.42	6.74		6.21		9.59		10.49		23.81	13.81		17.99	15.25

TOLYLENE DI-ISOCYANATE THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 2 TABLE 8 HR0001

BODYWEIGHTS - GROUP IV FEMALE

Batch 1 Actual day				0	1	4	5	6	7	8	11	12	13	14	15	18	19	20	21
Exposure day		Pre	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	PM
Cage 15	57	187	186	186	185	198	201	-	185	-	201	-	200	-	193	193	-	182	155
	58	184	181	185	187	203	205	-	196	-	206	-	205	-	175	177	-	147	0
	59	184	180	188	189	202	201	-	188	-	201	-	196	-	180	201	-	179	153
	60	185	182	192	193	204	203	-	185	-	202	-	202	-	185	195	-	184	157
Average		185.00	182.25	187.75	188.50	201.75	202.50		188.50		202.50		200.75		183.25	191.50		173.00	155.00
Standard deviation		1.41	2.63	3.10	3.42	2.63	1.91		5.2		2.38		3.77		7.68	10.25		17.45	2.00
Batch 2 Actual day				0	3	4	5	6	7	10	11	12	13	14	17	18	19	20	PM
Cage 16	61	183	183	184	200	204	201	-	192	-	200	-	193	-	196	174	-	0	0
	62	184	155	196	208	212	207	-	180	-	192	-	197	-	190	172	-	147	0
	63	164	170	171	177	182	180	-	164	-	179	-	172	-	156	150	-	0	0
	64	194	193	190	202	205	200	-	186	-	200	-	193	-	195	167	-	157	141
Average		178.75	195.25	185.25	196.75	200.75	197.00		180.50		192.75		188.75		184.25	165.75		152.00	141.00
Standard deviation		9.84	11.44	10.69	13.60	13.00	11.75		12.04		9.91		11.32		19.02	10.90		7.07	
Total average		181.87	183.75	186.50	192.63	201.25	199.75		184.50		197.63		194.75		183.75	178.63		166.00	151.50
Total standard deviation		7.32	7.85	7.41	10.18	8.70	8.33		9.59		8.47		10.11		13.44	16.89		17.62	7.19

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 3

TABLE 1

FOOD CONSUMPTION

(grams/rat/18hours)

MALES

	Group I			Group II			Group III			Group IV		
Day No	Batch I	Batch II	Group Mean	Batch I	Batch II	Group Mean	Batch I	Batch II	Group Mean	Batch I	Batch II	Group Mean
0	16	21	18.5	15	17	16	16	18	17	18	23	20.5
5	33	28	30.5	36	25	30.5	-	28	28	30	5	17.5
13	31	33	32	26	27	26.5	27	26	26.5	12	19	15.5
19	27	26	26.5	27	25	26	21	19	20	9	14	11.5

FEMALES

	Group I			Group II			Group III			Group IV		
Day No	Batch I	Batch II	Group Mean	Batch I	Batch II	Group Mean	Batch I	Batch II	Group Mean	Batch I	Batch II	Group Mean
0	13	14	13.5	19	17	18	14	16	15	16	18	17
5	30	22	26	27	22	24.5	27	21	24	25	9	17
13	26	24	25	22	22	22	25	24	24.5	14	13	13.5
19	23	22	22.5	19	20	19.5	15	12	13.5	11	5	8

TOLYLENE DI-ISOCYANATE
THREE WEEK INHALATION TOXICITY IN THE RAT
APPENDIX 3

TABLE 2 WATER CONSUMPTION
(mls/Rat/18 Hours)

MALES

Batch I	Batch II	Group I			Group II			Group III			Group IV		
Day No	Day No	Batch I	Batch II	Group mean	Batch I	Batch II	Group mean	Batch I	Batch II	Group mean	Batch I	Batch II	Group mean
0	0	19	21	20	20	15	17.5	19	14	16.5	16	19	17.5
5	5	29	29	29	31	27	29	28	27	27.5	28	5	16.5
* 13	12	27	27	29.5	28	24	26	28	25	26.5	12	20	16 *
19	19	37	37	28.5	24	20	22	20	20	20	11	22	16.5

FEMALES

Batch I	Batch II	Group I			Group II			Group III			Group IV		
Day No	Day No	Batch I	Batch II	Group mean	Batch I	Batch II	Group mean	Batch I	Batch II	Group mean	Batch I	Batch II	Group mean
0	0	17	16	16.5	20	20	20	19	19	19	18	20	19
5	5	32	30	31	31	25	28	33	21	27	29	12	20.5
* 13	12	28	27	27.5	26	25	25.5	32	26	29	16	16	16 *
19	19	25	17	21	33	19	26	21	21	21	17	17	17

* Means from 2 different days

REPORT NO: CTL/T/1286

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 4 - TABLES 1-16

TOLYLENE DI-ISOCYANATE SUB-ACUTE EXPOSURE

LUNG FUNCTION RESULTS

PAGES 56-72

TABLE 1

Days into Study: + 5 Days Treatment Group: I

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 1	801	148	1.8	266	0.13	0.07
	802	165	2.8	462	0.14	0.14
	803	185	2.6	481	0.13	0.16
	804	203	1.8	365	0.18	0.09
	$\bar{x}$	175	2.25	394	0.15	0.11
	SEM ±	12	0.26	49	0.01	0.02
Batch 2 ♂ Cage No 2	805	167	2.9	484	0.172	0.118
	806	153	2.7	413	0.125	0.09
	807	173	2.6	450	0.106	0.138
	808	157	2.7	424	0.172	0.118
	$\bar{x}$	163	2.73	443	0.144	0.108
	SEM ±	5	0.06	16	0.017	0.012
All ♂	$\bar{x}$	169	2.49	418	0.144	0.116
	SEM ±	6	0.88	26	0.009	0.01
Batch 1 ♀ Cage No.3	809	132	2.4	317	0.255	0.024
	810	165	2.8	462	0.233	0.1
	811	147	1.4	206	0.277	0.038
	812	185	2.1	389	0.325	0.078
	$\bar{x}$	157	2.18	343	0.272	0.06
	SEM ±	11	0.3	55	0.02	0.018
Batch 2 ♀ Cage No 4	813	172	2.4	413	0.244	0.058
	814	150	2.6	390	0.377	0.114
	815	177	2.4	425	0.287	0.057
	816	182	2.6	473	0.255	0.111
	$\bar{x}$	170	2.5	425	0.291	0.085
	SEM ±	7	0.06	18	0.03	0.016
All ♀'s	$\bar{x}$	164	2.34	384	0.282	0.073
	SEM ±	7	0.15	31	0.017	0.012
♂+ ♀	$\bar{x}$	166	2.41	401	0.213	0.094
	SEM ±	4.5	0.11	28	0.03	0.013

TABLE 2

Days into Study: Pre Exposure Treatment Group: II

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 5	817	140	3.0	420	0.23	0.08
	818	148	2.9	429	0.14	0.15
	819	160	2.4	384	0.21	0.16
	820	153	2.4	367	0.30	0.12
	$\bar{x}$	150	2.7	400	0.22	2
	SEM ±	4	0.2	15	0.03	0.02
Batch 2 ♂ Cage No 6	821	155	3.4	527	0.182	0.089
	822	162	2.5	405	0.134	0.097
	823	160	2.7	432	0.134	0.099
	824	120	1.6	192	0.106	0.054
	$\bar{x}$	149	2.55	389	0.139	0.084
	SEM ±	10	0.37	71	0.016	0.01
All ♂	$\bar{x}$	150	2.61	395	0.180	0.106
	SEM ±	5	0.19	33	0.023	0.013
Batch 1 ♀ Cage No 7	825	187	2.0	374	0.12	0.11
	826	187	2.4	449	0.14	0.12
	827	120	3.0	360	0.11	0.10
	828	145	2.9	421	0.14	0.10
	$\bar{x}$	160	2.6	401	0.13	0.110
	SEM ±	16	0.2	21	0.01	0.001
Batch 2 ♀ Cage No 8	829	162	2.5	405	0.106	0.061
	830	165	2.8	462	0.153	0.113
	831	170	2.0	340	0.143	0.054
	832	185	1.9	352	0.097	0.055
	$\bar{x}$	171	2.3	390	0.124	0.071
	SEM ±	5	0.21	28	0.014	0.014
All ♀'s	$\bar{x}$	165	2.42	395	0.126	0.089
	SEM ±	8	0.15	16	0.007	0.010
♂+ ♀	$\bar{x}$	157	2.53	395	0.153	0.098
	SEM ±	5	0.12	18	0.013	0.008

TABLE 3

Days into Study: Pre Exposure Treatment Group: III

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 9	833	110	2.2	242	0.12	0.043
	834	120	3.0	360	0.12	0.113
	835	120	2.2	264	0.13	0.133
	836	140	2.6	364	0.12	0.119
	$\bar{x}$	123	2.5	308	0.125	0.102
	SEM ±	26	0.2	32	0.004	0.02
Batch 2 ♂ Cage No 10	837	100	2.2	220	0.134	0.16
	838	160	2.1	336	0.143	0.071
	839	172	3.0	516	0.097	0.148
	840	154	2.5	385	0.124	0.095
	$\bar{x}$	147	2.45	364	0.125	0.12
	SEM ±	16	0.20	61	0.01	0.02
All ♂	$\bar{x}$	135	2.48	336	0.124	0.110
	SEM ±	13	0.18	48	0.007	0.01
Batch 1 ♀ Cage No 11	841	127	2.8	356	0.11	0.08
	842	160	2.6	416	0.14	0.11
	843	117	1.8	211	0.16	0.06
	844	155	2.8	434	0.10	0.09
	$\bar{x}$	156	2.5	354	0.13	0.09
	SEM ±	10	0.2	51	0.02	0.01
Batch 2 ♀ Cage No 12	845	193	2.6	502	0.143	0.114
	846	170	2.7	459	0.143	0.106
	847	107	1.3	139	0.172	0.065
	848	167	2.5	418	0.143	0.107
	$\bar{x}$	159	2.28	379	0.15	0.098
	SEM ±	10	0.33	82	0.007	0.011
All ♀'s	$\bar{x}$	150	2.39	367	0.139	0.092
	SEM ±	15	0.27	63	0.012	0.011
♂+ ♀	$\bar{x}$	142	2.43	351	0.131	0.101
	SEM ±	7	0.22	55	0.010	0.016

TABLE 4

Days into Study: Pre Exposure Treatment Group: IV

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 13	849	120	2.6	312	0.220	0.07
	850	63	3.6	227	0.17	0.06
	851	153	3.0	459	0.14	0.14
	852	180	2.2	396	0.15	0.17
	$\bar{x}$	129	2.85	348	0.17	0.11
	SEM ±	25	0.3	51	0.02	0.03
Batch 2 ♂ Cage No 14	853	170	2.9	493	0.134	0.158
	854	167	2.8	477	0.134	0.063
	855	105	1.8	189	0.115	0.059
	856	165	2.4	396	0.115	0.103
	$\bar{x}$	152	2.48	386	0.125	0.095
	SEM ±	16	0.25	69	0.005	0.023
All ♂	$\bar{x}$	140	2.66	369	0.147	0.103
	SEM ±	14	0.19	41	0.012	0.017
Batch 1 ♀ Cage No 15	857	145	3.2	464	0.13	0.11
	858	160	3.0	480	0.13	0.17
	859	163	2.2	359	0.12	0.05
	860	145	3.0	453	0.20	0.10
	$\bar{x}$	153	2.85	434	0.15	0.11
	SEM ±	5	0.22	27	0.02	0.02
Batch 2 ♀ Cage No 16	861	140	1.9	266	0.162	0.086
	862	155	3.0	465	0.172	0.083
	863	147	2.9	426	0.153	0.110
	864	142	2.9	412	0.172	0.086
	$\bar{x}$	146	2.68	392	0.165	0.093
	SEM ±	3	0.26	44	0.005	0.001
All ♀'s	$\bar{x}$	147	2.76	416	0.155	0.10
	SEM ±	5	0.16	25	0.010	0.012
♂+ ♀	$\bar{x}$	144	2.71	392	0.151	0.101
	SEM ±	7	0.12	24	0.011	0.010

TABLE 5

Days into Study: + 5 days. Treatment Group I

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂	802	150	2.4	360	0.162	0.064
Cage	802	150	2.2	330	0.337	0.051
No 1	803	177	2.3	407	0.070	0.071
	804	202	2.2	444	0.212	0.065
	$\bar{x}$	170	2.3	385	0.196	0.063
	SEM ±	13	0.5	25	0.056	0.004
Batch 2 ♂	805	185	3.2	592	0.143	0.106
Cage	806	170	2.6	442	0.223	0.086
No 2	807	155	2.9	450	0.435	0.060
	808	155	2.7	419	0.192	0.071
	$\bar{x}$	166	2.85	476	0.248	0.082
	SEM ±	7	0.13	39	0.064	0.009
All ♂	$\bar{x}$	168	2.56	431	0.222	0.072
	SEM ±	7	0.15	33	0.041	0.006
Batch 1 ♀	809	132	2.4	317	0.255	0.024
Cage	810	165	2.8	462	0.233	0.100
No 3	811	147	1.4	206	0.277	0.038
	812	185	2.1	389	0.325	0.078
	$\bar{x}$	157	2.2	343	0.272	0.060
	SEM ±	11	0.3	55	0.020	0.013
Batch 2 ♀	813	172	2.4	413	0.244	0.058
Cage	814	150	2.6	390	0.377	0.114
No 4	815	177	2.4	425	0.287	0.057
	816	182	2.6	473	0.255	0.111
	$\bar{x}$	170	2.5	425	0.291	0.085
	SEM ±	7	0.1	18	0.030	0.016
All ♀'s	$\bar{x}$	164	2.34	384	0.292	0.073
	SEM ±	7	0.15	31	0.017	0.012
♂ + ♀	$\bar{x}$	166	2.45	407	0.252	0.072
	SEM ±	5	0.17	29	0.032	0.009

TABLE 6

Days into Study: + 5 Days Treatment Group: II

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 5	817	163	2.8	456	0.266	0.122
	818	165	2.4	396	0.405	0.099
	819	160	2.6	416	0.172	0.078
	820	195	1.6	312	0.345	0.071
	$\bar{x}$	171	2.35	395	0.292	0.093
	SEM ±	8	0.26	30	0.049	0.011
Batch 2 ♂ Cage No 6	821	130	2.6	338	0.277	0.037
	822	143	2.4	343	0.391	0.053
	823	147	2.1	397	0.153	0.053
	824	145	2.4	348	0.420	0.067
	$\bar{x}$	141	2.53	357	0.310	0.052
	SEM ±	4	0.08	14	0.061	0.006
All ♂	$\bar{x}$	171	2.36	376	0.303	0.073
	SEM ±	6	0.13	17	0.037	0.01
Batch 1 ♀ Cage No 7	825	150	2.0	300	0.337	0.057
	826	173	2.1	363	0.289	0.071
	827	165	2.7	446	0.300	0.104
	828	155	2.5	388	0.212	0.101
	$\bar{x}$	161	2.33	374	0.285	0.083
	SEM ±	5	0.17	30	0.026	0.011
Batch 2 ♀ Cage No 8	829	165	2.7	446	0.223	0.35
	830	157	2.8	440	0.212	0.125
	831	173	1.8	311	0.325	0.08
	832	155	1.8	279	0.420	0.088
	$\bar{x}$	163	2.28	369	0.295	0.153
	SEM ±	4	0.28	43	0.097	0.07
All ♀'s	$\bar{x}$	162	2.3	372	0.290	0.118
	SEM ±	3	0.15	24	0.026	0.034
♂+ ♀	$\bar{x}$	159	2.33	374	0.297	0.095
	SEM ±	4	0.14	20	0.022	0.026

TABLE 7

Days into Study: + 5 Days Treatment Group: III

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 9	833	140	2.7	378	0.337	0.089
	834	170	2.8	476	0.233	0.053
	835	152	2.8	426	0.312	0.111
	836	155	1.9	295	0.363	0.051
	$\bar{x}$	156	2.55	394	0.312	0.076
	SEM ±	6	0.22	39	0.028	0.015
Batch 2 ♂ Cage No 10	837	165	2.2	363	0.244	0.074
	838	165	2.2	363	0.243	0.073
	839	175	2.8	490	0.172	0.063
	840	100	2.4	240	0.106	0.095
	$\bar{x}$	151	2.4	364	0.192	0.076
	SEM ±	17	0.14	51	0.033	0.007
All ♂	$\bar{x}$	153	2.48	379	0.251	0.076
	SEM ±	8	0.12	30	0.030	0.008
Batch 1 ♀ Cage No 11	841	150	3.0	450	0.266	0.031
	842	155	2.6	403	0.153	0.08
	843	165	2.4	396	0.212	0.054
	844	155	1.6	248	0.405	0.06
	$\bar{x}$	156	2.4	374	0.259	0.06
	SEM ±	3	0.29	44	0.054	0.012
Batch 2 ♀ Cage No 12	845	160	1.8	288	0.202	0.114
	846	150	2.6	390	0.391	0.094
	847	152	1.9	289	0.363	0.091
	848	150	2.5	375	0.266	0.121
	$\bar{x}$	153	2.2	335	0.306	0.105
	SEM ±	3	0.20	27	0.044	0.007
All ♀'s	$\bar{x}$	155	2.3	355	0.251	0.081
	SEM ±	3	0.17	12	0.030	0.011
♂+ ♀	$\bar{x}$	154	2.39	367	0.257	0.078
	SEM ±	2	0.10	19	0.022	0.006

TABLE 8

Days into Study: + 5 Days Treatment Group: IV

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 13	849	162	2.5	405	0.363	0.052
	850	150	1.9	285	0.405	0.041
	851	160	2.4	384	0.182	0.08
	852	150	2.6	330	0.255	0.075
	$\bar{x}$	156	2.35	351	0.304	0.062
	SEM ±	3	0.16	27	0.05	0.009
Batch 2 ♂ Cage No 14	853	113	2.4	271	0.212	0.030
	854	125	2.0	250	0.134	0.040
	855	150	2.4	360	0.350	0.125
	856	165	1.7	281	0.212	0.042
	$\bar{x}$	138	2.13	290	0.227	0.073
	SEM ±	12	0.17	24	0.045	0.019
All ♂	$\bar{x}$	132	2.24	321	0.266	0.067
	SEM ±	11	0.11	20	0.034	0.010
Batch 1 ♀ Cage No 15	857	143	2.4	343	0.115	0.049
	858	145	2.6	377	0.420	0.101
	859	120	2.9	348	0.450	0.100
	860	147	2.2	323	0.391	0.077
	$\bar{x}$	139	2.53	348	0.344	0.082
	SEM ±	6	0.15	11	0.077	0.012
Batch 2 ♀ Cage No 16	861	150	1.2	180	0.450	0.045
	862	175	1.8	315	0.244	0.069
	863	160	1.7	272	0.435	0.064
	864	160	2.0	320	0.363	0.080
	$\bar{x}$	161	1.68	272	0.373	0.057
	SEM ±	5	0.17	32	0.047	0.009
All ♀'s	$\bar{x}$	150	2.1	310	0.359	0.073
	SEM ±	6	0.19	21	0.042	0.007
♂+ ♀	$\bar{x}$	148	2.17	315	0.312	0.070
	SEM ±	4	0.44	14	0.029	0.006

TABLE 9

Days into Study: + 12 Days Treatment Group: I

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 1	801	123	2.4	295	0.223	0.058
	802	125	2.0	250	0.223	0.065
	803	107	2.2	235	0.153	0.099
	804	167	2.3	384	0.255	0.047
	$\bar{x}$	131	2.23	297	0.213	0.067
	SEM ±	13	0.09	33	0.021	0.01
Batch 2 ♂ Cage No 2	805	105	3.0	315	0.40	0.049
	806	100	2.8	280	0.15	0.129
	807	110	3.0	330	0.36	0.070
	808	110	2.4	264	0.27	0.087
	$\bar{x}$	106	2.8	297	0.30	0.084
	SEM ±	2	0.14	15	0.06	0.017
All ♂	$\bar{x}$	118	2.5	294	0.254	0.076
	SEM ±	8	0.13	17	0.032	0.01
Batch 1 ♀ Cage No 3	809	132	2.4	317	0.255	0.024
	810	165	2.8	462	0.233	0.1
	811	147	1.4	206	0.277	0.038
	812	185	2.1	389	0.325	0.078
	$\bar{x}$	157	2.18	343	0.272	0.06
	SEM ±	11	0.3	55	0.02	0.018
Batch 2 ♀ Cage No 4	813	155	2.8	434	0.36	0.053
	814	120	3.2	384	0.40	0.093
	815	120	2.8	336	0.29	0.056
	816	130	3.0	390	0.26	0.108
	$\bar{x}$	131	2.95	386	0.33	0.078
	SEM ±	8	0.1	20	0.032	0.014
All ♀'s	$\bar{x}$	144	2.56	365	0.3	0.069
	SEM ±	8	0.21	28	0.02	0.011
♂+ ♀	$\bar{x}$	131	2.54	329	0.277	0.072
	SEM ±	6	0.12	18	0.027	0.007

TABLE 10

Days into Study: + 12 Days Treatment Group: II

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 5	817	140	2.7	378	0.244	0.112
	818	95	2.2	209	0.300	0.048
	819	142	2.6	369	0.202	0.057
	820	160	2.2	209	0.337	0.063
	$\bar{x}$	134	2.48	291	0.28	0.07
	SEM ±	10	0.33	47	0.018	0.014
Batch 2 ♂ Cage No 6	821	125	2.5	313	0.28	0.097
	822	140	2.2	308	0.18	0.036
	823	115	2.2	253	0.30	0.064
	824	130	2.6	338	0.29	0.081
	$\bar{x}$	128	2.38	303	0.263	0.070
	SEM ±	5	0.10	18	0.028	0.013
All ♂	$\bar{x}$	131	2.4	297	0.267	0.070
	SEM ±	10	0.11	34	0.026	0.013
Batch 1 ♀ Cage No 7	825	165	1.7	281	0.162	0.122
	826	137	1.9	260	0.255	0.091
	827	155	2.2	341	0.244	0.082
	828	115	2.0	230	0.363	0.049
	$\bar{x}$	143	1.95	278	0.256	0.086
	SEM ±	6	0.05	12	0.021	0.008
Batch 2 ♀ Cage No 8	829	103	3.0	549	0.22	0.053
	830	140	3.2	448	0.30	0.037
	831	150	1.8	270	0.19	0.053
	832	145	2.2	319	0.32	0.093
	$\bar{x}$	155	2.55	397	0.258	0.059
	SEM ±	10	0.33	63	0.031	0.012
All ♀'s	$\bar{x}$	149	2.25	337	0.257	0.073
	SEM ±	7	0.20	38	0.024	0.010
♂+ ♀	$\bar{x}$	139	2.33	317	0.262	0.071
	SEM ±	5	0.10	22	0.015	0.007

TABLE 11

Days into Study: + 12 Days Treatment Group: III

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 9	833	135	2.2	297	0.377	0.07
	834	125	2.5	313	0.289	0.054
	835	120	2.4	288	0.192	0.048
	836	113	2.7	305	0.483	0.102
	$\bar{x}$	123	2.45	301	0.335	0.069
	SEM ±	5	0.10	5	0.06	0.012
Batch 2 ♂ Cage No 10	837	75	3.0	225	0.12	0.026
	838	140	3.6	504	0.45	0.054
	839	135	3.0	405	0.28	0.026
	840	125	3.2	400	0.24	0.054
	$\bar{x}$	119	3.2	384	0.27	0.043
	SEM ±	15	0.14	58	0.068	0.01
All ♂	$\bar{x}$	121	2.83	342	0.304	0.054
	SEM ±	7	0.16	31	0.044	0.009
Batch 1 ♀ Cage No 11	841	130	3.0	390	0.233	0.088
	842	137	1.8	247	0.350	0.049
	843	145	1.8	261	0.134	0.05
	844	167	2.0	334	0.106	0.073
	$\bar{x}$	145	2.15	308	0.206	0.065
	SEM ±	8	0.29	33	0.055	0.009
Batch 2 ♀ Cage No 12	845	105	2.0	210	0.29	0.076
	846	125	3.0	375	0.31	0.067
	847	130	3.0	390	0.24	0.074
	848	120	3.2	384	0.23	0.095
	$\bar{x}$	120	2.8	324	0.27	0.078
	SEM ±	3	0.27	26	0.019	0.006
All ♀'s	$\bar{x}$	132	2.48	324	0.237	0.072
	SEM ±	6	0.22	26	0.029	0.006
♂+ ♀	$\bar{x}$	127	2.66	333	0.270	0.062
	SEM ±	5	0.20	20	0.027	0.005

TABLE 12

Days into Study: + 12 Days Treatment Group: IV

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 13	849	100	2.7	270	0.617	0.083
	850	127	1.4	178	0.435	0.033
	851	140	1.6	224	0.466	0.063
	852	100	1.8	180	0.466	0.034
	$\bar{x}$	117	1.88	213	0.5	0.053
	SEM ±	10	0.29	22	0.04	0.012
Batch 2 ♂ Cage No 14	853	90	2.0	180	0.17	0.029
	854	105	2.2	231	0.223	0.041
	855	145	1.9	276	0.28	0.056
	856	93	1.4	130	0.23	0.023
	$\bar{x}$	108	1.86	204	0.225	0.037
	SEM ±	13	0.17	31	0.045	0.014
All ♂	$\bar{x}$	113	1.88	209	0.361	0.045
	SEM ±	7	0.15	18	0.055	0.007
Batch 1 ♀ Cage No 15	857	105	1.8	189	0.420	0.512
	858	142	1.9	270	0.277	0.075
	859	155	1.6	248	0.325	0.441
	860	100	1.9	190	0.466	0.067
	$\bar{x}$	126	1.8	224	0.372	0.274
	SEM ±	14	0.07	21	0.043	0.118
Batch 2 ♀ Cage No 16	861	110	1.8	198	0.62	0.044
	862	143	1.6	229	0.42	0.024
	863	170	1.6	272	0.42	0.056
	864	157	1.5	236	0.30	0.043
	$\bar{x}$	145	1.63	234	0.44	0.042
	SEM ±	13	0.06	15	0.066	0.013
All ♀'s	$\bar{x}$	135	1.71	229	0.406	0.158
	SEM ±	9	0.05	12	0.039	0.070
♂+ ♀	$\bar{x}$	124	1.79	219	0.383	0.102
	SEM ±	9	0.08	11	0.033	0.037

TABLE 13 -

Days into Study: + 19 Treatment Group: I

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 1	801	170	2.6	442	0.182	0.06
	802	90	2.2	198	0.337	0.06
	803	115	2.0	230	0.902	0.053
	804	150	2.4	360	0.575	0.059
	$\bar{x}$	131	2.3	308	0.499	0.058
	SEM ±	18	0.13	57	0.1	0.002
Batch 2 ♂ Cage No 2	805	155	3.5	558	0.255	0.125
	806	140	3.2	448	0.405	0.476
	807	130	3.4	442	0.300	0.083
	808	135	3.0	405	0.244	0.059
	$\bar{x}$	140	3.3	463	0.301	0.186
	SEM ±	4	0.13	33	0.37	0.098
All ♂	$\bar{x}$	136	2.8	385	0.400	0.122
	SEM ±	9	0.21	42	0.083	0.051
Batch 1 ♀ Cage No 3	809	150	2.4	360	0.435	0.053
	810	135	2.4	324	0.77	0.077
	811	150	2.4	360	0.596	0.146
	812	160	1.4	224	0.391	0.056
	$\bar{x}$	149	2.15	317	0.548	0.083
	SEM ±	5	0.25	32	0.086	0.022
Batch 2 ♀ Cage	813	150	2.2	330	0.312	0.068
	814	145	3.4	493	0.363	0.16
	815	150	2.6	390	0.255	0.108
	816	175	3.6	630	0.266	0.125
	$\bar{x}$	155	2.95	461	0.299	0.115
	SEM ±	7	0.33	66	0.025	0.038
All ♀'s	$\bar{x}$	158	2.55	389	0.424	0.099
	SEM ±	4	0.24	43	0.063	0.015
♂+ ♀	$\bar{x}$	144	2.68	387	0.412	0.111
	SEM ±	5	0.16	29	0.05	0.026

TABLE 14

Days into Study: + 19 Days Treatment Group: II

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 5	817	135	3.2	432	0.688	0.04
	818	150	3.4	510	0.300	0.053
	819	125	3.2	400	0.518	0.095
	820	150	2.8	420	0.363	0.065
	$\bar{x}$	140	2.9	441	0.467	0.063
	SEM ±	6	0.66	24	0.087	0.012
Batch 2 ♂ Cage No 6	821	130	3.2	416	0.289	0.136
	822	120	2.0	240	0.289	0.033
	823	80	2.8	224	0.391	0.130
	824	130	3.8	494	0.244	0.05
	$\bar{x}$	115	2.95	344	0.303	0.088
	SEM ±	12	0.377	66	0.031	0.027
All ♂	$\bar{x}$	128	3.05	392	0.385	0.075
	SEM ±	8	0.27	53	0.075	0.020
Batch 1 ♀ Cage No 7	825	135	2.0	270	0.377	0.04
	826	180	2.6	468	0.312	0.056
	827	140	3.0	420	0.289	0.114
	828	135	3.2	432	0.266	0.083
	$\bar{x}$	148	2.7	395	0.311	0.073
	SEM ±	11	0.26	42	0.024	0.016
Batch 2 ♀ Cage No 8	829	150	3.4	510	0.518	0.036
	830	130	2.8	364	0.312	0.065
	831	125	1.2	150	0.518	0.036
	832	165	1.4	231	0.337	0.05
	$\bar{x}$	143	2.2	314	0.348	0.047
	SEM ±	9	0.54	79	0.062	0.007
All ♀'s	$\bar{x}$	145	2.45	356	0.366	0.06
	SEM ±	9	0.41	63	0.050	0.014
♂+ ♀	$\bar{x}$	136	2.75	374	0.376	0.088
	SEM ±	11	0.13	57	0.061	0.04

TABLE 15

Days into Study: + 19 Days Treatment Group: III

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 9	833	130	3.6	468	0.35	0.058
	834	125	3.4	425	0.363	0.053
	835	105	3.2	336	0.312	0.06
	836	120	3.6	432	0.466	0.077
	$\bar{x}$	120	3.45	415	0.373	0.062
	SEM ±	5	0.1	28	0.033	0.005
Batch 2 ♂ Cage No 10	837	110	2.8	308	0.277	0.091
	838	100	2.0	200	0.289	0.063
	839	105	2.4	252	0.419	0.079
	840	105	3.0	315	0.312	0.167
	$\bar{x}$	105	2.55	274	0.324	0.10
	SEM ±	2	0.22	32	0.033	0.023
All ♂	$\bar{x}$	113	3.0	342	0.349	0.081
	SEM ±	4	0.02	33	0.023	0.013
Batch 1 ♀ Cage No 11	841	130	3.8	494	0.391	0.119
	842	150	3.2	480	0.287	0.080
	843	140	3.2	448	0.391	0.050
	844	135	2.6	351	0.363	0.038
	$\bar{x}$	139	3.2	443	0.358	0.072
	SEM ±	4	0.25	32	0.025	0.018
Batch 2 ♀ Cage No 12	845	150	2.8	420	0.337	0.06
	846	125	1.0	125	0.513	0.06
	847	150	3.0	450	0.391	0.06
	848	130	3.5	460	0.255	0.06
	$\bar{x}$	139	2.6	364	0.375	0.06
	SEM ±	7	0.56	80	0.055	0
All ♀'s	$\bar{x}$	139	2.90	404	0.367	0.060
	SEM ±	4	0.30	43	0.028	0.009
♂+ ♀	$\bar{x}$	126	2.95	373	0.353	0.073
	SEM ±	4	0.18	27	0.018	0.008

TABLE 16

Days into Study: + 130days Treatment Group: IV

	Rat No	Rate bpm	Tidal Vol mls	Minute Vol mls	Resistance mls/sec-ml cm H_2O	Compliance mls/cm H_2O
Batch 1 ♂ Cage No 13	849	90	1.6	144	0.483	0.065
	850	110	1.8	198	0.640	0.087
	851	65	1.2	78	0.391	0.060
	852	95	1.6	152	0.617	0.040
	$\bar{x}$	90	1.55	143	0.533	0.063
	SEM ±	9	0.13	25	0.059	0.01
Batch 2 ♂ Cage No 14	853	35	0.6	21	0.596	0.05
	854	125	1.0	125	0.596	0.063
	855	110	1.6	125	0.555	0.042
	856	75	2.0	150	0.377	0.055
	$\bar{x}$	86	1.3	118	0.531	0.052
	SEM ±	20	0.31	34	0.052	0.004
All ♂	$\bar{x}$	88	1.43	124	0.532	0.058
	SEM ±	10	0.16	19	0.036	0.005
Batch 1 ♀ Cage No 15	857	85	1.4	119	0.555	0.095
	858	85	1.4	119	0.500	0.065
	859	105	1.6	168	0.391	0.053
	860	125	1.2	150	0.337	0.063
	$\bar{x}$	100	1.4	139	0.446	0.069
	SEM ±	10	0.08	12	0.050	0.009
Batch 2 ♀ Cage No 16	861	Died before test completion			0.714	
	862	70	0.8	56	0.663	0.016
	863	100	0.6	60	0.575	0.023
	864	130	0.8	104	0.800	0.033
	$\bar{x}$	100	0.73	73.3	0.688	0.024
	SEM ±	17	0.067	15	0.047	0.005
All ♀'s	$\bar{x}$	100	1.11	110	0.567	0.050
	SEM ±	8	0.14	16	0.056	0.01
♂+ ♀	$\bar{x}$	94	1.28	121	0.549	0.054
	SEM ±	7	0.11	13	0.032	0.006

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 5

TABLE 1 URINALYSIS - MALES

Batch No	Group	Volume (ml)	pH	Specific Gravity	Protein mg/rat	Glucose	Bilirubin	Comments
1	1	28.0	6.0	1.043	15.96	-ve	-ve	
2	1	26.0	6.0	1.047	13.39	-ve	-ve	Blood in sample
1	2	32.0	6.5	1.032	11.20	-ve	-ve	Blood in sample
2	2	20.0	6.0	1.048	10.50	-ve	-ve	Blood in sample
1	3	12.5	6.0	1.049	7.78	-ve	-ve	
2	3	20.0	6.0	1.044	9.05	-ve	-ve	
1	4	9.0	6.0	1.048	0.54	-ve	-ve	Trace of blood
2	4	4.0	6.0	1.032	0.00	-ve	-ve	Blood in sample

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 5

TABLE 2 URINALYSIS - FEMALES

Batch No	Group	Volume (ml)	pH	Specific Gravity	Protein mg/rat	Glucose	Bilirubin	Comments
1	1	25.0	6.0	1.041	1.44	-ve	-ve	
2	1	20.0	6.0	1.044	0.38	-ve	-ve	
1	2	30.0	6.5	1.032	2.10	-ve	-ve	Blood in sample
2	2	11.0	6.0	1.038	0.77	-ve	-ve	Blood in sample
1	3	3.5	6.0	1.048	0.00	-ve	-ve	
2	3			NO SAMPLE				
1	4			NO SAMPLE				
2	4	4.5*	6.0	1.040	0.00	-ve	-ve	One rat died in cage

*Only one rat

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 6

TABLE 1 BLOOD BIOCHEMISTRY - GROUP I MALES

Batch No	Rat No	Urea (mg/100ml)	ALT (mU/ml)	Sodium (mg/100ml)	Potassium (mg/100ml)	AST (mU/ml)
1	01	33	8	347	25	23
	02	32	11	340	25	47
	03	37	6	350	23	I/S
	04	41	12	345	28	I/S
	$\bar{x}$	35.8	9.3	345.5	25.3	35.0
	SEM	2.1	1.4	2.1	1.0	6.9
2	05	46	10	345	20	41
	06	48	15	347	20	67
	07	51	I/S	340	19	I/S
	08	44	14	352	21	34
	$\bar{x}$	47.3	13.0	346.0	20.0	47.3
	SEM	1.5	1.5	2.5	0.4	10.0
Group overall	$\bar{x}$	41.5	10.9	345.8	22.6	42.4
	SEM	2.5	1.2	1.5	1.1	7.36

I/S = Insufficient Sample

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 6 - continued

TABLE 2 BLOOD BIOCHEMISTRY - GROUP II MALES

Batch No	Rat No	Urea (mg/100ml)	ALT (mU/ml)	Sodium (mg/100ml)	Potassium (mg/100ml)	AST (mU/ml)
1	17	42	8	345	20	35
	18	47	6	352	21	37
	19	35	7	343	24	44
	20	34	I/S	I/S	I/S	I/S
	$\bar{x}$	39.5	7.0	346.7	21.7	38.7
	SEM	3.1	0.6	2.7	1.2	2.7
2	21	47	7	345	23	36
	22	38	8	347	24	43
	23	47	14	340	20	59
	24	46	13	343	21	48
	$\bar{x}$	44.5	10.5	343.8	22	46.5
	SEM	2.2	1.8	1.5	0.9	4.8
Group overall	$\bar{x}$	42.0	9.0	345.0	21.9	43.1
	SEM	2.0	1.2	1.4	0.7	3.2

I/S Insufficient Sample

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 6 - continued

TABLE 3 BLOOD BIOCHEMISTRY - GROUP III MALES

Batch No	Rat No	Urea (mg/100ml)	ALT (mU/ml)	Sodium (mg/100ml)	Potassium (mg/100ml)	AST (mU/ml)
1	33	55	8	350	20	34
	34	39	7	345	25	53
	35	37	8	340	21	57
	36	47	8	340	23	40
	$\bar{x}$	44.5	7.8	343.8	22.3	46.0
	SEM	4.1	0.3	2.4	1.1	5.4
2	37	43	10	347	20	40
	38	45	12	345	19	42
	39	41	10	347	19	46
	40	44	10	345	23	44
	$\bar{x}$	43.3	10.5	346.0	20.3	43.0
	SEM	0.9	0.5	0.6	0.9	1.3
Group overall	$\bar{x}$	43.9	9.1	344.9	21.3	45.5
	SEM	2.0	0.6	1.2	0.8	2.6

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 6 - continued

TABLE 4 BLOOD BIOCHEMISTRY - GROUP IV MALES

Batch No	Rat No	Urea (mg/100ml)	ALT (mU/ml)	Sodium (mg/100ml)	Potassium (mg/100ml)	AST (mU/ml)
1	49	46	12	347	25	52
	50	91	66	343	20	195
	51	79	I/S	I/S	I/S	I/S
	52	54	10	352	23	54
	$\bar{x}$	67.5	29.3	347.3	22.7	100.3
	SEM	10.5	18.4	2.6	1.5	47.4
2	53		No sample			
	54	I/S	15	I/S	I/S	68
	55	80	I/S	I/S	I/S	I/S
	56	84	I/S	I/S	I/S	I/S
	$\bar{x}$	82.0	15.0	-	-	68.0
	SEM	2.0	-	-	-	-
Group overall	$\bar{x}$	72.3	25.8	347.3	22.7	92.3
	SEM	7.3	13.5	2.6	1.5	34.4

I/S Insufficient Sample

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 6 - continued

TABLE 4 BLOOD BIOCHEMISTRY - GROUP I FEMALES

Batch No	[illegible] No	Urea (mg/100ml)	ALT (mU/ml)	Sodium (mg/100ml)	Potassium (mg/100ml)	AST (mU/ml)
1	09	55	8	347	27	31
	10	46	9	I/S	I/S	46
	11	43	7	340	23	38
	12		No sample			
	$\bar{x}$	48.0	8.0	343.5	25.0	38.3
	SEM	3.6	0.6	3.5	2.0	4.3
2	13	57	6	347	20	34
	14	48	6	345	23	36
	15	57	7	350	19	46
	16	70	7	347	21	36
	$\bar{x}$	58.0	6.5	347.3	20.8	38.0
	SEM	4.5	0.3	1.0	0.9	2.7
Group overall	$\bar{x}$	53.7	7.1	346.0	22.2	38.1
	SEM	3.4	0.4	1.4	1.2	2.2

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 6 - continued

TABLE 6 BLOOD BIOCHEMISTRY - GROUP II FEMALES

Batch No	Rat No	Urea (mg/100ml)	ALT (mU/ml)	Sodium (mg/100ml)	Potassium (mg/100ml)	AST (mU/ml)
1	25	52	8	345	23	62
	26		No sample			
	27	49	6	340	22	40
	28	49	8	340	19	51
	$\bar{x}$	50.0	7.3	341.6	21.3	51.0
	SEM	1.0	0.7	1.7	1.2	6.4
2	29	54	8	340	20	46
	30	63	8	345	20	34
	31	73	7	343	19	38
	32	61	9	347	24	43
	$\bar{x}$	62.8	8.0	343.8	20.8	40.3
	SEM	3.9	0.4	1.5	1.1	2.7
Group overall	$\bar{x}$	57.3	7.7	342.9	21.0	44.9
	SEM	3.3	0.4	1.1	0.8	3.5

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 6 - continued

TABLE 7 BLOOD BIOCHEMISTRY - GROUP III FEMALES

Batch No	Rat No	Urea (mg/100ml)	ALT (mU/ml)	Sodium (mg/100ml)	Potassium (mg/100ml)	AST (mU/ml)
1	41	46	7	340	23	50
	42	54	6	334	20	44
	43	54	5	352	22	38
	44		No sample			
	$\bar{x}$	51.3	6.0	342.0	21.7	44.0
	SEM	2.7	0.6	5.3	0.9	3.5
2			No sample			
	46	58	I/S	I/S	I/S	I/S
	47		No sample			
	48	49	7	347	21	47
	$\bar{x}$	53.5	7.0	347.0	21.0	47.0
	SEM	4.5	-	-	-	-
Group overall	$\bar{x}$	52.2	6.3	34.75	21.5	44.8
	SEM	2.1	0.5	3.81	0.6	2.6

I/S Insufficient sample

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 6 - continued

TABLE 3 BLOOD BIOCHEMISTRY - GROUP IV FEMALES

Batch No	Rat No	Urea (mg/100ml)	ALT (mU/ml)	Sodium (mg/100ml)	Potassium (mg/100ml)	AST (mU/ml)
1	57	51	17	347	19	74
	58		No sample			
	59		No sample			
	60	58	11	345	24	55
	$\bar{x}$	54.5	14.0	346.0	21.5	64.5
	SEM	3.5	3.0	1.0	2.5	9.5
2	61		No sample			
	62		No sample			
	63		No sample			
	64		No sample			
	$\bar{x}$					
	SEM					
Group overall	$\bar{x}$	54.5	14.0	346.0	21.5	64.5
	SEM	3.5	3.0	1.0	2.5	9.5

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 7

LUNG WEIGHTS - MALES

TABLE 1

Group I

Batch I				Batch II			
Rat No	Body wt (g)	Lung wt (g)	Lung % Body	Rat No	Body wt (g)	Lung wt (g)	Lung % Body
801	263	1.338	0.509	805	303	1.565	0.517
802	252	1.556	0.617	806	265	1.218	0.460
803	268	1.309	0.488	807	282	1.368	0.485
804	278	1.536	0.553	808	267	1.323	0.496
$\bar{x}$	265	1.435	0.542		279	1.016	0.490
SEM	5	0.065	0.029		9	0.288	0.012
				Group mean	272	1.402	0.516
				SEM	5	0.047	0.017

Group II

Batch I				Batch II			
Rat No	Body wt (g)	Lung wt (g)	Lung % Body	Rat No	Body wt (g)	Lung wt (g)	Lung % Body
817	281	1.347	0.479	821	255	1.223	0.480
818	274	1.247	0.455	822	250	1.353	0.541
819	280	1.447	0.517	823	261	1.391	0.533
820	245	1.183	0.483	824	255	1.546	0.606
$\bar{x}$	270	1.306	0.484		255	1.378	0.540
SEM	8	0.058	0.013		2	0.066	0.026
				Group mean	263	1.342	0.512
				SEM	5	0.043	0.017

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 7 - continued

LUNG WEIGHTS - MALES

TABLE 2

Group III

Batch I				Batch II			
Rat No	Body wt (g)	Lung wt (g)	Lung % Body	Rat No	Body wt (g)	Lung wt (g)	Lung % Body
833	244	1.485	0.609	837	241	1.339	0.556
834	253	1.491	0.589	838	239	1.230	0.515
835	253	1.423	0.562	839	239	1.311	0.549
836	272	1.761	0.643	840	279	1.525	0.547
$\bar{x}$	256	1.540	0.602		250	1.351	0.542
SEM	6	0.075	0.018		10	0.062	0.009
				Group mean	253	1.446	0.572
				SEM	5	0.058	0.015

Group IV

Batch I				Batch II			
Rat No	Body wt (g)	Lung wt (g)	Lung % Body	Rat No	Body wt (g)	Lung wt (g)	Lung % Body
849	187	1.506	0.805	853	-	-	-
850	157	1.561	0.994	854	196	1.718	0.877
851	156	1.675	1.074	855*	172	1.758	1.022
852	185	1.497	0.809	856	180	1.570	0.872
$\bar{x}$	171	1.560	0.921		183	1.682	0.924
SEM	9	0.041	0.068		7	0.057	0.049
				Group mean	176	1.612	0.922
				SEM	6	0.039	0.041

*Blood taken before weighing

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 7 - continued

LUNG WEIGHTS - FEMALES

TABLE 3

Group I

Batch I				Batch II			
Rat No	Body wt (g)	Lung wt (g)	Lung % Body	Rat No	Body wt (g)	Lung wt (g)	Lung % Body
809	206	1.101	0.534	813	227	1.226	0.540
810	202	1.132	0.560	814	233	1.200	0.515
811	211	1.112	0.527	815	211	-	-
812	220	1.259	0.572	816	202	1.244	0.616
$\bar{x}$	210	1.151	0.548		218	1.223	0.557
SEM	4	0.037	0.011		7	0.013	0.030
				Group mean	214	1.182	0.552
				SEM	4	0.025	0.013

Group II

Batch I				Batch II			
Rat No	Body wt (g)	Lung wt (g)	Lung % Body	Rat No	Body wt (g)	Lung wt (g)	Lung % Body
825	203	1.178	0.580	829	212	1.185	0.559
826	192	1.046	0.545	830	204	1.171	0.574
827	213	1.203	0.565	831	208	1.019	0.490
828	190	1.998	0.525	832	191	1.077	0.564
$\bar{x}$	200	1.106	0.554		204	1.113	0.547
SEM	5	0.050	0.012		5	0.039	0.019
				Group mean	202	1.110	0.550
				SEM	3	0.029	0.011

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 7 - continued

LUNG WEIGHTS - FEMALES

TABLE 4

Group III

Batch I				Batch II			
Rat No	Body wt (g)	Lung wt (g)	Lung % Body	Rat No	Body wt (g)	Lung wt (g)	Lung % Body
841	244	1.485	0.609	837	241	1.339	0.556
842	253	1.491	0.589	838	239	1.230	0.515
843	253	1.423	0.562	839	239	1.311	0.549
844	272	1.761	0.643	840	279	1.525	0.547
$\bar{x}$	256	1.540	0.601		250	1.351	0.542
SEM	7	0.075	0.017		10	0.062	0.009
				Group mean	253	1.446	0.572
				SEM	5.	0.058	0.015

Group IV

Batch I				Batch II			
Rat No	Body wt (g)	Lung wt (g)	Lung % Body	Rat No	Body wt (g)	Lung wt (g)	Lung % Body
857	155	1.360	0.877	861	-	-	-
858	-	-	-	862	-	-	-
859	153	1.659	1.084	863	-	-	-
860	157	1.619	.031	864	141	1.593	1.130
$\bar{x}$	155	1.546	0.997		141	1.593	1.130
SEM	1	0.094	0.062		-	-	-
				Group mean	152	1.558	1.031
				SEM	4	0.067	0.055

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 8

ANALYTICAL DETAILS OF TEST COMPOUND

Batch No:	ABH2146
Colour (Hazenunits):	10
Strength (MW = 174.2):	100%
Hydrolysable chlorine:	0.0068%
Total chlorine:	0.02%
Acidity (AS HCl):	022%
Isomer ratio:	2.4 isomer

TOLYLENE DI-ISOCYANATE
THREE WEEK INHALATION TOXICITY IN THE RAT
APPENDIX 9
SUMMARY OF MAJOR HISTOPATHOLOGICAL FINDINGS IN NASAL PASSAGES, LARYNX, TRACHEA, LUNGS, CERVICAL LYMPH NODES SALIVARY GLANDS, SPLEEN AND THYMUS

Tissue/Pathological finding	Male				Female			
	Group				Group			
	I	II	III	IV	I	II	III	IV
Number of animals examined/group	8/8	8/8	8/8	6/8	8/8	8/8	8/8	8/8
Nasal passages: Number examined	8	8	8	8	8	8	8	8
Mild/moderate acute rhinitis	0	8	4	0	0	6	5	0
Epithelial degeneration	0	8	3	0	0	7	6	0
Necrotising rhinitis - moderate	0	0	4	0	0	0	3	0
marked	0	0	0	8	0	0	0	8
Epithelial hyperplasia	0	7	8	8	0	8	8	8
Squamous metaplasia	0	1	3	8	0	2	4	8
Submucosal chronic inflammatory infiltration	0	0	4	0	0	0	3	0
Focal chronic rhinitis	0	0	0	0	1	0	0	0
Larynx: Number examined	7	8	7	7	6	7	7	8
Focal epithelial degeneration/necrosis	0	0	0	2	0	0	0	3
Epithelial hyperplasia	0	1	4	4	0	2	6	4
Squamous metaplasia	0	1	1	4	0	0	2	4
Submucosal chronic inflammatory (lymphocytic) infiltration	0	0	5	0	1	0	2	0
Mild/acute laryngitis	0	3	0	2	0	0	1	4
Inflammatory debris in lumen	0	0	1	2	0	0	1	4
Trachea: Number examined	7	8	8	5	7	7	7	7
Epithelial degeneration/necrosis	0	0	2	1	0	0	0	6
Epithelial hyperplasia	0	1	5	4	0	1	4	6
Submucosal chronic inflammatory infiltration	0	1	5	0	0	0	0	0
Mild acute tracheitis	0	0	3	3	0	0	1	3
Inflammatory debris in lumen	0	0	1	1	0	0	0	3

TOLYLENE DI-ISOCYANATE
THREE WEEK INHALATION TOXICITY IN THE RAT
APPENDIX 9 - continued
SUMMARY OF MAJOR HISTOPATHOLOGICAL FINDINGS IN NASAL PASSAGES, LARYNX, TRACHEA, LUNGS, CERVICAL LYMPH NODES SALIVARY GLANDS, SPLEEN AND THYMUS

Tissue/Pathological finding	Male				Female			
	Group				Group			
	I	II	III	IV	I	II	III	IV
Lung: Number examined	8	8	8	8	8	8	8	8
Necrotising bronchitis/bronchiolitis								
slight	0	0	4	6	0	0	5	5
marked	0	0	0	1	0	0	0	3
Bronchial/bronchiolar dilatation	0	0	1	7	0	0	2	8
Peribronchial/bronchiolar chronic inflammatory infiltration	0	1	7	7	0	0	8	5
Peribronchial/bronchiolar epithelial hyperplasia	0	2	8	8	0	0	8	8
Polyp formation/submucosal fibrous proliferation	0	0	1	0	0	0	3	4
Goblet cell differentiation	0	0	0	1	0	0	0	0
Bronchial squamous epithelial metaplasia	0	0	0	5	0	0	0	5
Bronchial/bronchiolar debris/plugging	0	0	5	8	0	0	4	7
Bronchiolar/alveolar collapse	0	0	3	2	0	0	1	6
Alveolar oedema/fibrin/hyaline body formation	0	0	1	8	0	0	2	7
Alveolar histiocytosis	1	1	4	7	0	2	8	8
Chronic interstitial infiltration and/or fibrosis	0	0	0	4	0	0	2	6
Alveolar epithelialisation	0	0	0	3	0	0	0	2
Acute alveolitis/neutrophilia	0	0	2	5	0	0	2	3
Mild/acute bronchitis/bronchiolitis	0	1	0	1	0	0	0	0
Peribronchiolar/perivascular neutrophilia	0	0	2	1	0	1	2	2
Peribronchal/bronchiolar lymphocytic accumulations/								
infiltration; some slight to moderate	3	5	5	0	1	4	7	1
moderate to marked	0	1	3	1	0	1	1	1
Focal chronic bronchitis/bronchiolitis	0	4	4	0	0	2	4	0
Perivascular chronic inflammatory (lymphocytic) infiltration	0	0	0	0	1	0	2	0

TOLYLENE DI-ISOCYANATE
THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 9 - continued

SUMMARY OF MAJOR HISTOPATHOLOGICAL FINDINGS IN NASAL PASSAGES, LARYNX, TRACHEA, LUNGS, CERVICAL LYMPH NODES SALIVARY GLANDS, SPLEEN AND THYMUS

Tissue/Pathological finding	Male				Female			
	Group				Group			
	I	II	III	IV	I	II	III	IV
Cervical lymph node: Number examined	5	8	7	7	8	8	8	7
Slight focal acute lymphadenitis	0	1	1	1	0	0	2	1
Haemorrhage/erythrophagocytosis	0	0	1	0	0	0	2	0
Salivary glands: Number examined	7	8	8	8	8	8	7	8
Sialoadenitis	0	0	1	1	0	0	0	2
Spleen: Number examined	8	8	8	8	8	8	8	8
Small/shrunken	0	0	0	7	0	0	0	7
Haemopoiesis - minimal	0	0	2	7	0	3	3	8
moderate/makred	3	0	0	0	4	0	0	0
Thymus: Number examined	8	8	8	8	8	8	8	6
Moderate/marked involution	0	0	0	8	0	0	0	6

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 10

COMPOSITION OF STOCK DIET

	%
Finely ground barley	26.34
Maize meal	9.11
Bran	18.08
Sussex ground oats	18.30
White fishmeal (crude protein 66%)	4.46
Yeast	1.34
Dried skimmed milk (crude protein 33%)	13.17
Fine meat and bone meal (crude protein 50%)	8.71
Salt	0.45
'Nuclo' P No 7 + B_2	0.04
	100.00

TOLYLENE DI-ISOCYANATE

THREE WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 11

LABORATORY TEMPERATURE

Day Number	Max (°F)	Min (°F)
0	80	64
1	80	64
4	80	54
5	not recorded	
6	80	64
7	82	68
8	82	68
11	72	69
12	not recorded	
13	not recorded	
14	not recorded	
15	not recorded	
16	72	60
17	72	60
18	70	62
19	72	62
20	76	64
21	76	64

TOLYLENE DI-ISOCYANATE
THREE-WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 12

HAEMATOLOGY PARAMETERS : DAY 21 FEMALE

	HB g/dl	Hct (PCV)	RBC X10^12/l	MCV fl.	MCH pg.	MCHC g/dl	PLT X10^9/l	WBC	DIFFERENTIAL NEUT X10^9/l	LYMP X10^9/l	MONO X10^9/l	EOSI X10^9/l	BASO X10^9/l	PT sec	KCT sec
GROUP 1															
MEAN	16.1	.448	7.83	57.	20.4	36.0	763	7.5	1.1	5.9	.4	.0	.0	14.2	16.4
STD. DEV'N	.7	.021	.34	1.	.4	.6	62.	1.2	.3	1.3	.2	.0	.0	.3	2.1
SAMPLES.	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
GROUP 2															
MEAN	16.0	.434	7.63	57.	20.8	36.9**	753	8.7	1.2	7.0	.5	.1	.0	13.7	17.1
STD. DEV'N	.7	.015	.31	1.	.2	.5	99.	1.2	.5	1.0	.2	.1	.0	.8	2.8
SAMPLES.	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
GROUP 3															
MEAN	16.0**	.456	8.00	57.	20.8	36.8**	758	8.6	.8**	7.4*	.4	.0	.0	13.8	16.1
STD. DEV'N	.4	.013	.31	2.	.5	.5	162.	1.9	.2	1.8	.3	.0	.0	1.2	2.6
SAMPLES.	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
GROUP 4															
MEAN	18.5**	.479	8.91**	54.**	20.5	38.4**	731	6.1	1.3	4.4	.4	.0	.0	14.8*	19.1
STD. DEV'N	.6	.024	.42	1.	.3	.7	191.	1.5	.7	1.4	.3	.0	.0	.2	5.5
SAMPLES.	4	4	4	4	4	4	4	4	4	4	4	4	4	2	2

TOLYLENE DI-ISOCYANATE
THREE-WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 12 - continued

HAEMATOLOGY PARAMETERS : DAY 21 MALE

	HB g/dl	Hct (PCV)	RBC X10^12/l	MCV fl.	MCH pg.	MCHC g/dl	PLT X10^9/l	WBC	DIFFERENTIAL NEUT X10^9/l	LYMP X10^9/l	MONO X10^9/l	EOSI X10^9/l	BASO X10^9/l	PT sec	KCT sec
GROUP 1															
MEAN	17.1	.470	8.26	57.	20.5	36.3	774	11.9	1.8	8.5	.7	.0	.0	17.1	18.7
STD. DEV'N	.8	.026	.40	2.	.7	.6	82.	1.7	.6	1.2	.3	.1	.0	3.4	3.2
SAMPLES.	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
GROUP 2															
MEAN	17.0	.462	8.11	57.	20.8	36.7	746	9.4	1.2	7.5	.5	.1	.0	24.3*	26.7**
STD. DEV'N	.8	.026	.53	1.	.5	.8	81.	1.0	.6	.3	.3	.1	.0	6.1	6.6
SAMPLES.	6	8	8	8	8	8	8	8	8	8	8	8	8	8	8
GROUP 3															
MEAN	17.3	.467	8.34	56.	20.5	37.0*	757	9.0*	1.0**	7.6	.4	.1	.0	21.1	23.0
STD. DEV'N	.8	.026	.43	2.	.4	.6	89.	1.2	.1	1.2	.2	.0	.0	8.5	9.1
SAMPLES.	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
GROUP 4															
MEAN	19.4**	.514**	9.49**	55.**	20.5	37.7**	555**	5.5	1.1**	4.0**	.3**	.0	.0	16.1	19.5
STD. DEV'N	1.1	.039	1.13	1.	1.0	1.0	101.	1.8	.7	1.4	.3	.1	.0	2.4	4.9
SAMPLES.	7	7	7	7	7	7	7	7	7	7	7	7	7	4	4

TOLYLENE 81-ISOCYANATE
THREE-WEEK INHALATION TOXICITY IN THE RAT

APPENDIX 12 - continued

HAEMATOLOGY PARAMETERS : DAY 21

	HB g/dl	Hct (PCV)	RBC X10^12/l	MCV fl.	MCH pg.	MCHC g/dl	PLT X10^9/l	WBC	DIFFERENTIAL NEUT	LYMP	MONO	EOSI	BASO	PT sec	KCT
GROUP 1															
MEAN	16.6	.459	8.05	57.	20.5	36.1	768	9.2	1.5	7.2	.6	.0	.0	15.6	17.6
STD. DEV'N	.9	.026	.42	2.	.6	.6	70.	2.3	.6	1.8	.3	.1	.0	2.8	2.8
SAMPLES.	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16
GROUP 2															
MEAN	16.5	.448	7.87	57.	20.8	36.8**	750	9.0	1.2	7.3	.5	.1 *	.0	19.0	21.9*
STD. DEV'N	.9	.025	.49	1.	.4	.7	87.	1.1	.5	.8	.3	.1	.0	6.9	6.9
SAMPLES.	16	16	16	16	16	16	16	16	16	16	16	16	16	16	16
GROUP 3															
MEAN	17.1	.462	8.18	57.	20.6	36.9**	758	8.8	.9**	7.5	.4	.0	.0	17.7	19.8
STD. DEV'N	.7	.021	.41	2.	.5	.5	123.	1.5	.2	1.4	.2	.0	.0	7.1	7.5
SAMPLES.	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
GROUP 4															
MEAN	19.1**	.501**	9.28**	54.**	20.5	38.0**	619**	5.7**	1.2	4.2**	.3*	.0	.0	15.7	19.3
STD. DEV'N	1.0	.037	.95	1.	.8	.9	158.	1.6	.7	1.3	.2	.1	.0	2.0	4.5
SAMPLES.	11	11	11	11	11	11	11	11	11	11	11	11	11	6	6

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